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MOLD FUNGI IN THE ETIOLOGY OF RESPIRATORY ALLERGIC DISEASES

IX. Further Studies with Mold Extracts

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IN previously evaluated extracts, consideration was given to certain modifications of the mold material prior to extraction, to subsequent treatment of a preliminary aqueous extract, and even to the culture broth itself.[1,2] In the spring of 1945, the preparation and study of more experimental extracts of *Alternaria tenuis* were undertaken. These were prepared from Alternaria grown in malt extract broth (Difco), which medium has been used throughout all our work since 1939.

PREPARATION OF EXTRACTS 13-32

The detailed technique of preparing the extracts studied will be the subject of a separate communication. In general, to a preliminary aqueous extract were added successive equal volumes of cold acetone. Even though precipitation was usually immediate after each addition of acetone, the mixtures were allowed to stand in the cold (—20° C.) for twenty-four hours for complete reaction before separation in a refrigerated centrifuge. Most precipitation occurred at 50 and 75 per cent by volume acetone concentration, but faint additional precipitate could be detected even after 93 per cent acetone concentration had been exceeded. Grossly, the precipitates usually appeared as fine to coarse flocculent, or "oily," occasionally gummy. The flocculent precipitates were in general lighter in color than those with

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TABLE I. TESTS WITH EXTRACTS 13-32

Ext. No.	Type of Precipitate	% Acetone by Volume	INTRADERMAL TESTS 1/100,000 Patients Tested	1/100,000 Reaction	1/100,000 %	1/10,000 Tested	1/10,000 Reaction	1/10,000 %	1/1,000 Tested	1/1,000 Reaction	1/1,000 %	1/100 Tested	1/100 Reaction	1/100 %	PUNCH (SCRATCH) 1/50 Tested	1/50 Reaction	1/50 %
A13	oil	50	38	26	68	37	32	87	36	32	89	22	21	95	10	8	80
14	floc.	75x75x50	32	13	41	31	20	65	38	25	66	25	23	92	10	1	10
15		75x75x75	30	8	27	29	12	41	39	19	49	25	23	92	10	3	30
32	oil	75x75x87	18	1	7	17	1	6	13	4	31	11	5	45	4	2	50
17	oil	75x87	30	1	3	31	6	20	39	11	44	26	20	77	10	1	10
19	oil	75x93	30	2	7	29	6	20	39	10	26	26	18	69	10	1	10
16	oil	87	30	2	7	29	2	7	39	5	13	26	10	38	10	1	10
20	floc.	87	30	2	7	29	1	3	39	7	18	26	12	46	10	0	0
18	oil	93	30	2	7	29	0	0	39	3	8	26	14	54	10	0	0
B21	floc.	50	30	9	30	29	15	52	37	19	51	25	21	84	10	0	0
23	oil	75x50	30	6	20	29	14	48	38	18	47	25	20	80	10	1	10
22	crystals	75x50	30	2	7	29	3	10	38	8	21	26	12	46	10	0	0
24	floc.	75x50	30	2	7	29	4	14	38	3	8	26	13	50	10	0	0
28	floc.	75x75	18	3	17	17	10	59	14	10	71	11	10	91	4	3	75
29	oil	75x75	18	0	0	17	1	6	13	4	31	11	4	36	4	3	75
30	floc.	75x87	18	4	22	17	6	35	13	10	71	11	6	55	4	3	75
31	oil	75x87	18	0	0	17	2	12	13	2	15	11	3	27	4	4	100
25	oil	87	30	2	7	29	3	10	38	5	13	25	11	44	10	0	0
26	floc.	87	30	0	0	29	0	0	38	2	5	26	10	39	10	0	0
27		93	30	4	13	29	5	17	38	0	0	26	13	50	10	0	0

x—Re-precipitated

the dark brown oily appearance. Whereas the flocculent precipitates usually appeared immediately, the oily material often began as an opalescent appearance of the supernatant, from which minute globules eventually began to settle out; after centrifugation, the oily precipitates formed a stratum on the bottom, leaving the supernatant clear. Sometimes both an oily and flocculent precipitate occurred simultaneously but could be stratified by repeated centrifugation, following which the oily layer could be decanted along with the supernatant, and separated from the latter in a separatory funnel. After aqueous solution some precipitates were further fractionated by re-precipitation. In this manner nine precipitates were obtained. (*A*, Table I).

Following a slightly modified technique another preliminary aqueous extract was separated into eleven acetone-precipitable fractions. In this series further separation of more of the re-dissolved precipitates was accomplished. (*B*, Table I).

After removal of all acetone the precipitates were dissolved in a minimal amount of water and distributed to tared Erlenmeyer flasks in which they were quick-frozen and dried by lyophilization. The dried material was dissolved in Hollister-Stier solution in a ratio of 1/50, and sterilized by Seitz filtration. The extracts thus prepared were denoted by numbers 13 to 32, and distributed to our membership for skin testing on Alternaria-sensitive patients.

SKIN TESTING WITH EXTRACTS 13-32

In Table I are shown the results of direct skin testing by both the punch (scratch) and intradermal methods. Skin reactive principles are seen to be

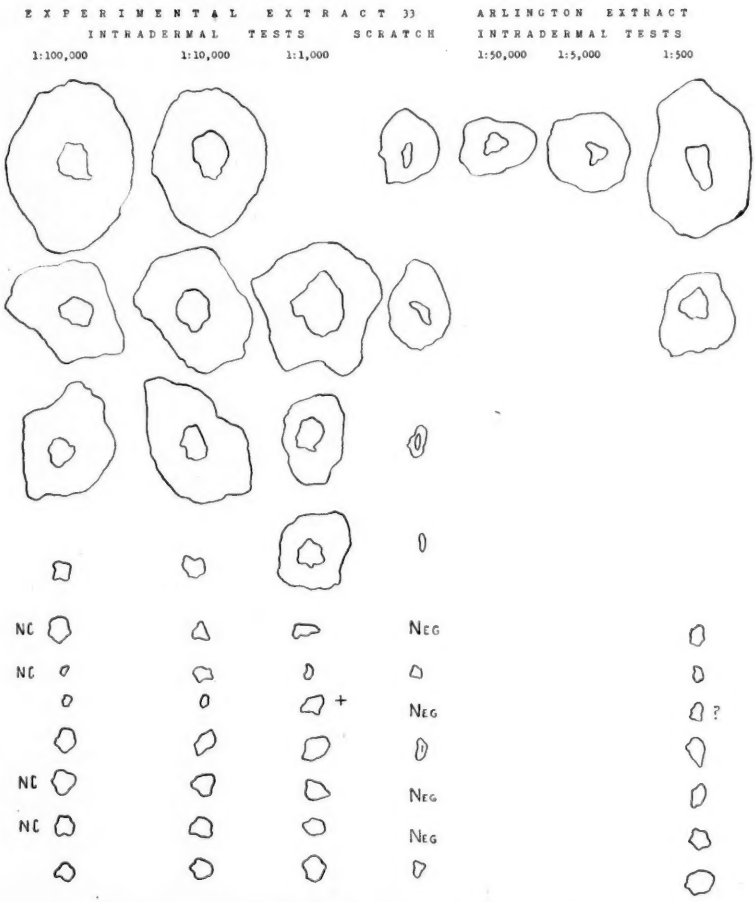

Fig. 1. Tracings of reactions to extract 33 and to a commercial extract (Arlington) in five patients sensitive to Alternaria, two sensitive to other substances, and four normal persons.
N.C. = normal control. (S.E.)

present in all the experimental extracts, indicating that no clear-cut separation into reactive and non-reactive fractions was obtained. This was not entirely unexpected, since the various precipitates had been obtained empirically with varying acetone concentrations, and might not necessarily represent *distinct* fractions. Generally, however, those fractions precipitated with an acetone concentration of 75 per cent or less seem more reactive than those obtained with greater amounts of acetone, suggesting that the allergen is almost although not completely precipitated by 75 per cent acetone. On the other hand, there is no clear difference in skin reactivity determined by the appearance of the precipitate unless the results with extracts 28 and

TABLE II. COMPARATIVE TESTING ALTERNARIA EXTRACT 33

INTRADERMAL TESTS (SCRATCH) PUNCH

1/100,000		1/10,000		1/1,000		1/100	1/50		
Extract 33	Regular Method Extract	Extract 33	Regular Method Extract	Extract 33	Regular Method Extract	Regular Method Extract	Extract 33	Regular Method Extract	
+	++	++	++	++++	++++		+	+++	H.E.P.
+++	+	++++	++	++++	++++	++++	++	+	H.E.P.
++	+	++++	++		+++		+++	+	H.E.P.
+		++++		+++		+	++	−	H.E.P.
+		+		+++		++++	+	−	H.E.P.
+		++		++ "x"		++	+	+	H.E.P.
+++	−	+++	+	++++	++	+++	+	−	H.E.P.
++	−	++++	+		+++			+	H.E.P.
+		++++			+	++			H.E.P.
+++		++++			+++	+			H.E.P.
−		+	−	+	+	+++			H.E.P.
+		+++		++++	+++	+++			H.E.P.
+++		+++		++++		+++		−	H.E.P.
+	−	+++	−	++++	++++	++++	++	+	H.E.P.
−		++		++++	+++	++++	+++	−	H.E.P.
−		+++		++++	−		−	+	L.D.H.
−		−		++	−		−	−	L.D.H.
++++		++++		+++++	+++		−	++	L.D.H.
							++++	+	L.D.H.
−		−		++	−		−	−	
Patients Tested 19 Reacted 14 74%		Patients Tested 19 Reacted 17 89%		Patients Tested 15 Reacted 15 100%			Patients Tested 14 Reacted 10 71%		

"x" Test caused asthma

TABLE III. TESTS ON ALTERNARIA-SENSITIVE PATIENTS

INTRADERMAL TESTS 1/1,000		SCRATCH TESTS	
Hollister-Stier	33	Hollister-Stier	33
++	+++ "x"	++	++
++	++	++	++
+++	++	+++	++
++	++	++	++
++	++	++	++
++	++	++	++
++	++	++	++
++	++	++	++
+	++ "x"	++	++ "x"
		++	++
		++	++
		++	++
		++	++
		+	++

"x"—Sensitive only to Alternaria

TESTS ON ALLERGIC PATIENTS SENSITIVE TO OTHER FACTORS THAN ALTERNARIA

Patients Tested	6	6	19	19
Positive Reactions	0	0	0	0
Negative Reactions	6	6	19	19

K.D.F.

30, both of which were derived from flocculent precipitates, may suggest that re-precipitation concentrates the antigen (compare extracts 29 and 31 both of which were made from oily precipitates). The results of the intradermal tests with 1/100 dilution cannot be accepted for studying any differences in the extract, but they do reveal the presence of antigen even in those extracts which did not possess a high reaction titre.

PREPARATION OF EXPERIMENTAL EXTRACT 33

Following the studies outlined above, which revealed the presence of antigen in precipitates obtained by all concentrations of acetone from 50 to 93 per cent by volume, we proceeded to prepare experimental extract 33 to include *all* fractions precipitable by an excess of the reagent. Accordingly, a general technique of adding nine volumes of cold acetone to a preliminary aqueous extract with rapid stirring was followed. The exact technique still in process of definition will be published in the near future. The mixture was placed in the cold (—20° C) for twenty-four hours, after which all the precipitate was collected by centrifugation. After removal of the acetone, the precipitate was dissolved in water, lyophilized, and dissolved in Hollister-Stier solution in the ratio of 1/50. This extract was distributed to various members of our group for skin testing on Alternaria-sensitive patients.

SKIN TESTING WITH EXTRACT 33

In Table II are shown the results of intradermal and punch (scratch) tests on Alternaria-sensitive patients with extract 33, as well as with our "regular method" extract. One of us (K.D.F.) tested a series of allergic patients both sensitive and non-sensitive to Alternaria with extract 33 and with a commercial product (Hollister-Stier) (Table III). Figure 1 shows the tracings of reactions to extract 33 and to another commercial extract (Arlington) in five patients sensitive to Alternaria, two sensitive to other substances, and four normal persons.

Most of these tests suggest the superiority of extract 33; especially in Table II and Fig. 1 do higher dilutions of extract 33 produce equal or greater reactions than the other extracts under comparison. Unfortunately, it was impossible to include extract 33 in the series dealing with extracts 13 to 32 discussed earlier in this paper. However, the percentage of positive reactions for each dilution of extract 33 is slightly greater than for the corresponding dilutions of extract 13, the only other extract approaching 33 in reactivity. Furthermore, since in dilution of 1/1,000 extract 33 reacted on 100 per cent of Alternaria-sensitive patients, whereas extract 13 reacted in only 89 per cent in similar dilution, and in 95 per cent of cases in a tenfold (1/100) concentration, this slight difference has added significance.

CONCLUSION

Variations in acetone precipitation of a preliminary aqueous extract of Alternaria are presented. Skin tests on Alternaria-sensitive patients suggest that precipitation with nine volumes of acetone gives an extract of higher potency than any experimental extract previously studied by us.

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THE USE OF ANTIHISTAMINIC DRUGS IN HUMAN TUBERCULOSIS

A Preliminary Report

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PRIMARY tuberculosis is characterized, in the great majority of cases, by its relative benignity and absence of tissue destruction. These characteristics are reversed in the reinfection or secondary phase. This reversal is dependent upon hypersensitivity to an antigen which is developed during the primary phase and maintained as long as tubercle bacilli remain within the body. Upon reinfection or spread of the bacilli from a primary site, there occurs an inflammatory reaction, which is characterized by exudation and may be followed by caseation necrosis.[7] If this acute inflammation could be prevented, a significant advance in tuberculosis therapy would be achieved. It seemed possible that antihistaminic drugs might protect sensitized cells from injury and thus alter the course of the disease. This preliminary report is concerned with the effects of antihistaminic drugs upon human tuberculosis.

The drugs* employed, as the salts, were diphenhydramine (Benadryl), tripelennamine (Pyribenzamine), phenindamine (Thephorin), and thonzylamine (Neohetramine). Patients were started on 50 mg. of the antihistamine three times daily. The dose was increased to 300-400 mg. per day, as tolerated. The highest daily dose given any patient was 500 mg., and the longest period of administration was seven months. Benadryl and Pyribenzamine were first used, but they were not well tolerated in large doses. When it was necessary to discontinue a drug because of side effects, patients were transferred to Neohetramine because it is reported to be less toxic than other available antihistaminics.[1-6,8-10] It is evident that the least toxic drug should always be used, but this is especially true in an already toxic patient, particularly one fighting the insult of an acute exudative or pneumonic lesion. No significant changes were observed in the urine, erythrocyte sedimentation rate or differential leukocyte count. A moderate increase in pulse rate was almost always noted after institution of therapy.

Patients presenting pulmonary and non-pulmonary manifestations of tuberculosis were studied. Among the patients presenting pulmonary manifestations of the disease were cases of tuberculous pneumonia, acute exudative cases, mixed exudative and fibrotic cases, and advanced chronic fibrotic cases. A total of thirty patients is presented in this preliminary report. The type of disease and the results obtained are presented in Table

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*We are indebted to Wyeth, Incorporated, for the supply of Neohetramine, manufactured by the Nepera Chemical Co., Inc., and to Hoffman-LaRoche for the supply of Thephorin.

TABLE I.
RESULTS OF ANTIHISTAMINE THERAPY IN PULMONARY TUBERCULOSIS*

Type of Lesion	No. Cases	Cough			Sputum			Weight			"Well-Being"			X-Ray Lesions (Densities)			Chest Pain			Appetite			Temperature			Mantoux Reaction	
		Increase	Decrease**	No Change	Increase	Decrease	No Change	Increase	Decrease	No Change	Increase	Decrease	No Change	Increase	Decrease	No Change	Increase	Decrease	No Change	Increase	Decrease	No Change	Increase	Decrease	No Change	Conversion to Negative	Not Converted
Exudative and T.B. Pneumonia (Acute)	6 2 — 8	0	7	1	0	7	1	6	2	0	7	0	1	0	7	1	0	2	4	5	0	3	1	3	4	6	2
Mixed—(Productive and Exudative)	14	1	9	4	1	9	4	8	2	4	10	1	3	1	4	9	0	4	10	6	0	8	0	2	12	11	3
Productive (Fibrosing)	8	2	2	4	2	2	4	1	4	3	1	1	6	1	0	7	0	0	8	0	2	6	0	0	8	7	1
Totals	30	3	18	9	3	18	9	15	8	7	18	2	10	2	11	17	0	6	22	11	2	17	1	5	24	24	6

*All patients received at least 10 weeks of drug treatment.
**In most instances thinning and almost complete absence of sputum was observed.

I. Physical findings have been omitted, so frequently, they do not parallel the roentgenological findings. Four case abstracts illustrate the effect of antihistaminic drugs.

Case 1.—M.R., A 24-year-old colored woman, was admitted October 29, 1947, following a four-month history of weight loss, anorexia and one episode of hemoptysis. On admission her only symptoms were a slight cough and a negligible amount of sputum. The x-rays revealed scattered infiltrations irregularly throughout both lung fields without evidence of excavation. Sputum was negative on the first two examinations but positive on the third. The blood showed: RBC, 4,860,000 Hb. 12 Gm. (79 per cent), WBC 6,200, with a normal differential; and sedimentation rate 14 mm. in sixty minutes. Urine was normal by routine examination. This patient was placed on bed rest. Several attempts at artificial pneumothorax found the pleural space obliterated.

She was apparently running a satisfactory course (Fig. 1) with only occasionally positive sputum, when six months following admission she suddenly became febrile (temperature 104° F.), had a sudden drop in weight, loss of appetite and severe prostration. She was placed in a quiet room. As she was too ill to transport to the X-Ray Department, a portable film was taken at the bedside. This showed the left side to be obliterated by a dense homogeneous shadow (Fig. 2). Four days following this acute episode, April 24, 1948, she was placed on Pyribenzamine. The initial dose was 200 mg. daily. When the dose was elevated, she became dizzy and nauseated, so the initial dose was maintained. The Mantoux test† at the onset of medication was plus 2. She had lost nine pounds in the one week prior to medication. After one week of antihistaminics, her temperature was normal. She no longer lost weight. Her malaise was quickly disappearing. By the third week she had improved to the point where she was placed back in the ward. Her appetite had returned. Her Mantoux test was still plus 2. She had gained two pounds. Her cough had lessened, and her sputum had thinned considerably, but had not diminished

†P.P.D. first strength was used throughout this series except for one patient who required the second strength.

Fig. 1. Case 1. M.R., black, female, aged twenty-four. Roentgenogram taken February 18, 1948 reveals moderately advanced tuberculosis in both lung fields.

Fig. 2. Case 1. Bedside roentgenogram taken April 22, 1948, twenty-four hours following the acute onset of a left tuberculous pneumonia, accompanied by high fever (104 F.), chest pain and marked prostration. Antihistamines were started after this view was taken.

Fig. 3. Case 1. Roentgenogram taken May 17, 1948, after twenty-one days on antihistamines. Temperature was normal after the first week of therapy. By the time this view was taken the patient was well enough to be removed from the quiet room and was placed back on the ward. Note marked clearing of the entire left side. No definite evidence of excavation or fluid is seen.

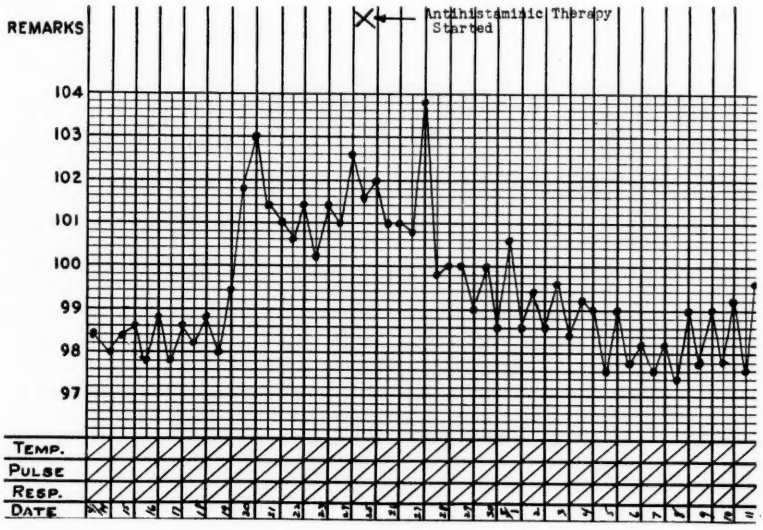

Chart 1. M.R. The temperature elevation in this case reflects the sudden onset of the acute tuberculous involvement. It is well to note that such an elevation does not always accompany an acute dissemination of the infection and similarly that a normal temperature range can exist in the presence of an acute progression of the disease process. See Chart 3. (April 14 to May 11, 1949.)

in quantity. By the fifth week her Mantoux test had diminished to plus 1, and by the seventh week was negative. The Mantoux findings did not remain negative, however, but became intermittently positive (never more than plus 1). X-Ray revealed considerable clearing of the left side by one month (Fig. 3). The patient's vigor had returned considerably. She was kept on 200 mg. daily of Pyribenzamine for thirteen weeks. It was discontinued because of increasing nausea and palpitation. During this period she had regained seven pounds and toward the end of it had no cough whatsoever. Her sputum, likewise, had disappeared and what she could force up was negative for tubercle bacilli.

This patient received no antihistamine for the next eighteen weeks. Her cough gradually increased, and she began to produce a greenish-yellow tenaceous sputum. The Gaffky count was plus 2 on two occasions when she was not taking antihistamine therapy. She lost two pounds during the first month. These were regained after a few weeks. She ran irregular bouts of elevated temperature, reaching 101.4° F. and tachycardia. Roentgenograms revealed an extension of the lesions in the right upper lung field. There were no significant urine or blood changes except for marked increase in the sedimentation rate (from 14 to 27 mm. Cutler method). Antihistamines were again administered. Pyribenzamine caused restlessness and insomnia as well as nausea, and it was replaced by Neohetramine, 150 mg. daily. This dose was gradually increased until a maintenance dose of 350 mg. daily was obtained. The patient, to date, has been on this second course of drug for seven weeks. Her cough again has markedly decreased, and she now produces only one-fourth the quantity of sputum that was expectorated at the onset of this second course. The sputum has thinned considerably but remains positive for tubercle bacilli continuously and contains occasional blood streaks. The Mantoux test is constantly positive (plus 1). Roentgenogram reveals new lesions which appeared in

Fig. 4. Case 2. V.J.M. Admission roentgenogram taken July 20, 1948. This 26-year-old white woman had a six-month course of streptomycin, one to three grams daily, one year prior to admission, without benefical results. A large cavity can be seen in the left lung just above the dense area of tuberculous pneumonia.

Fig. 5. Case 2. Roentgenogram taken after one month on antihistamines. There is considerable clearing of the left lower lobe as well as some of the exudative reaction in the upper lobe on this same side.

Fig. 6. Case 2. Routine roentgenogram taken five months after the onset of Neohetramine therapy. The left lung continues to clear, the right lung remains clear.

the interval between the first and second courses of antihistamine drug. The sedimentation rate remains 27 mm. in thirty minutes. There have been no significant changes in the blood picture or urine analysis of this patient.

Case 2.—V.J.M., A 26-year-old white woman, was admitted June 2, 1948, with a history of pulmonary tuberculosis of one and one-half years. One year prior to admission to this institution, she had received 1 to 3 grams of streptomycin daily for six months without evidence of improvement. She had received no therapy other than bed rest for six months preceding the present admission. Laboratory findings were as follows: Sedimentation rate 20 mm. in sixty minutes; red blood cells 4,100,000; hemoglobin 12.5 Gm. (82 per cent); white blood cells 10,400; differential normal; sputum Gaffky count, plus 4, plus 6, and plus 4; vital capacity 2 liters; weight 112 pounds. Roentgenogram of the chest showed a large cavity in the left upper lung and pneumonic consolidation in the left lower lobe (Fig. 4).

The temperature following admission ran between 98.2° and 103° F. The patient appeared ill. Because of the exudative nature of her lesion and the obvious toxicity, she was considered a candidate for antihistamine therapy (Chart 2).

Pyribenzamine was given daily in doses of 150 mg., but because of undesirable side effects she was placed on Neohetramine. Doses up to 350 mg. daily were maintained without untoward effects. Her general feeling of well-being was considerably improved. She was obviously less toxic. Her appetite, however, had not yet returned. She was losing weight slowly. The roentgenogram showed evidence of parenchymal clearing (Fig. 5). After five months on Neohetramine therapy, she had improved considerably in all ways except that her appetite was still very poor and there had been a gradual loss of weight to 102 pounds. Her sputum remained positive. The Mantoux skin test had changed from a plus 2 at the onset of medication, to negative in eight weeks. Bi-monthly Mantoux tests have remained negative to date, with the exception of two faint reactions. Roentgenograms of the chest showed further clearing of the left lung (Fig. 6).

To date there have been no significant blood or urinary changes. It is a notable fact that the disease continued to progress despite prolonged treatment with streptomycin. Progression was halted, and the exudative lesions began to clear after Neohetramine was given.

Case 3.—V.L., A 20-year-old Mexican woman, was admitted January 21, 1948, with the diagnosis of bilateral pulmonary tuberculosis with cavitation. At no time prior to admission had this patient complained of symptoms referable to the chest or to the disease. A survey roentgenogram discovered these lesions. On admission, the sputum Gaffky count was plus 6, plus 7, plus 4. There were no significant urinary findings. The blood showed: red blood cells 4,920,000; hemoglobin 11 Gm. (73 per cent), white blood cells 15,300, with a normal differential count; sedimentation rate 28 mm. in sixty minutes. Vital capacity was 1.5 liters. Almost immediately following admission, she developed a cough which produced enough thick yellowish sputum to cover the bottom of her sputum box. Roentgenograms of the lungs on admission revealed lesions which were classified as far advanced, exudative in type, and bilaterally apical in location. Several small cavities were present in the apices of both lungs (Fig. 7). The patient was placed on bed rest. In a month's time, it became obvious that the course was of a down-grade nature. Her cough increased, sputum increased in quantity and continued positive for tubercle bacilli. She became obviously toxic with symptoms of pain in the chest, loss of weight, sweats, and an irregular, low grade fever ranging between 97° and 100° F.

On April 19, 1948, administration of 150 mg. of Pyribenzamine daily was begun. In one week, the dose was increased to 200 mg. daily. At subsequent weekly intervals, the dose was increased until a dosage of 400 mg. was taken daily. The Mantoux

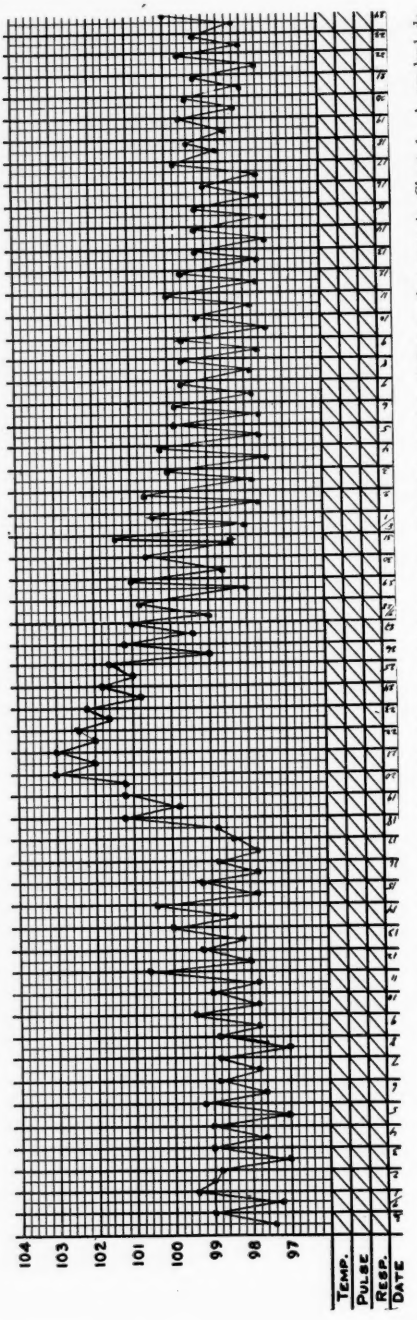

Chart 2. Temperature record of V.J.M. from May 30 to July 24, 1949, illustratinq a type of febrile reaction similar to that seen in Chart 1. A gradual decrease was noted after the administration of antihistaminic therapy following the sudden temperature rise seen in the center of the chart.

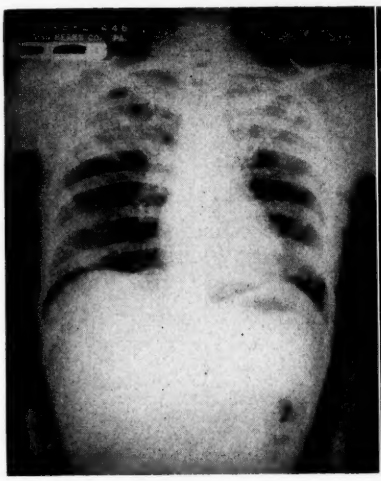

Fig. 7. Case 3. Admission film of V.L., a Mexican woman, aged twenty. Multiple excavations are seen in the right and left upper lobes. Clinical course was on the down-grade with weight loss and obvious toxicity.

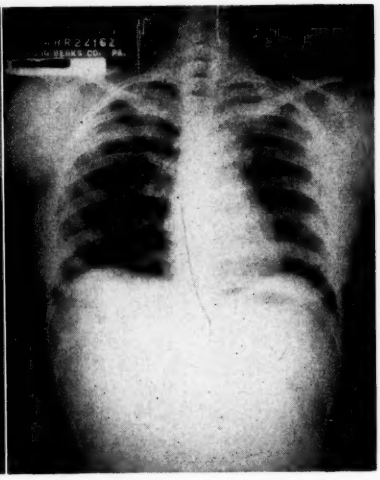

Fig. 8. Case 3. After one month on antihistamines. Exudative phase of lesions is greatly diminished. Excavations bilaterally considerably diminished, many having completely disappeared. Clinical course reversed. Weight gain obvious on the film.

skin test prior to the initial dose was 3 plus. Two weeks following the onset of medication, the Mantoux test was 2 plus. Two weeks later it was still 2 plus. However, during the sixth week, the test was negative, and with the exception of one faint reaction, it remained negative for ten weeks (five tests). During the sixteen weeks of antihistaminic therapy, symptoms of toxicity disappeared rapidly. The patient ate well and she gained thirteen pounds during this period. Her temperature became normal in two weeks and was never elevated above 99° F. A Roentgenogram (Fig. 8), taken one month following the administration of the first dose of antihistamine drug, revealed marked clearing of the exudative lesions in both lung fields, and the cavity in the right upper lung field had almost disappeared. No urinary or blood changes were noted. Two repeat sedimentation rates were both 26 mm. in sixty minutes. The sputum Gaffky count dropped to plus 3, then plus 2. Her general feeling of well-being increased remarkably. Cough and sputum were almost negligible. After sixteen weeks, medication was discontinued. During the period of administration of the drug no side effects presented themselves which could be related to the antihistamine.

One week following the discontinuance of the drug, the patient began to cough more frequently, and her sputum began to increase; the Gaffky count became plus 4. The Mantoux reaction returned positive (plus 2) in ten days. For the first time in her life, she experienced amenorrhea. The pulse became elevated with a rate between 100 and 108 beats per minute. Her appetite began to disappear and she lost seven pounds in weight. The Mantoux test remained persistently positive. The patient's course was obviously down-hill. The x-ray revealed a spread of the lesions (Fig. 9). After thirteen weeks without antihistamines, she was again placed on Pyribenzamine, 150 mg. daily. The dose was gradually increased, as before, until a total of 350 mg. were being taken daily. She began to complain of dizziness after five weeks on this schedule. Pyribenzamine was discontinued, and she was immediately placed on Thephorin therapy. She received a daily dose of 200 mg. of this drug. Two weeks following the reinstitution of antihistamine medication her cough was practically

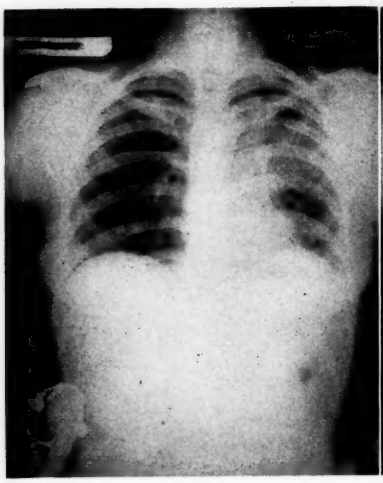

Fig. 9. Case 3. Roentgenogram taken two months following the discontinuance of antihistamine therapy. Considerable spread of the lesions can be seen in the mid-lung field on the left. This was accompanied by amenorrhea and a return of the symptoms of toxicity.

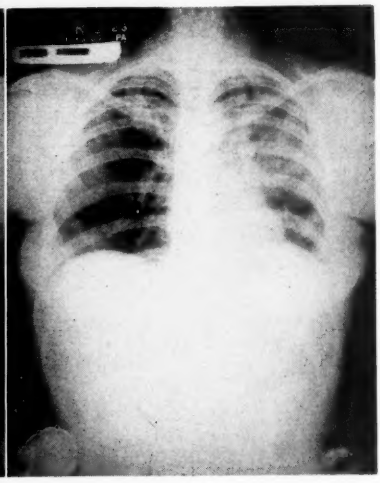

Fig. 10. Case 3. Roentgenogram taken after one month on the second course of antihistamines. The spread seen in the left lung field can be seen to have cleared. Amenorrhea ceased. Clinical course again reversed.

absent and only slight in the morning. At this time, she produced a small amount of sputum which had turned from a thick, yellowish to a thin, whitish appearance. She menstruated for the first time in nearly four months. The Mantoux test was plus 1. Her appetite increased and she gained two pounds during the first two weeks. The lesions again began to decrease (Fig. 10). At the present time this patient is continuing her second course of antihistamines. During the entire course thus far no significant changes have been noted in the routine blood and urine studies.

Among the extrapulmonary group was one case each of laryngeal and glandular tuberculosis, and one case of erythema nodosum. The first patient presented a laryngeal tuberculosis (Type IV, Grade IV), causing severe pain and hoarseness for a period of six months. This patient was treated with dramatic symptomatic relief which persisted until the patient died as a result of a massive pulmonary hemorrhage. A second patient presented an axillary gland involvement as a complication in a case of a stabilized and apparently arrested pulmonary tuberculosis.

Case 4.—K.W., aged twenty-six, white, female, housewife, giving no clinical history referable to the respiratory system was first seen at another hospital complaining of a mass in the left axilla. This mass was removed surgically, examined microscopically, and found to be tuberculous. A roentgenogram of the chest was then made, and a minimal pulmonary tuberculosis was discovered. She was soon thereafter admitted to the Hamburg Sanatorium.

On admission here the clinical history and physical examination were essentially negative or non-contributory except for a well-healed axillary scar.

The laboratory findings were as follows: Hemoglobin 91 per cent; red blood cells 5,660,000; white blood cells 11,100; polynuclear neutrophiles 48 per cent; small

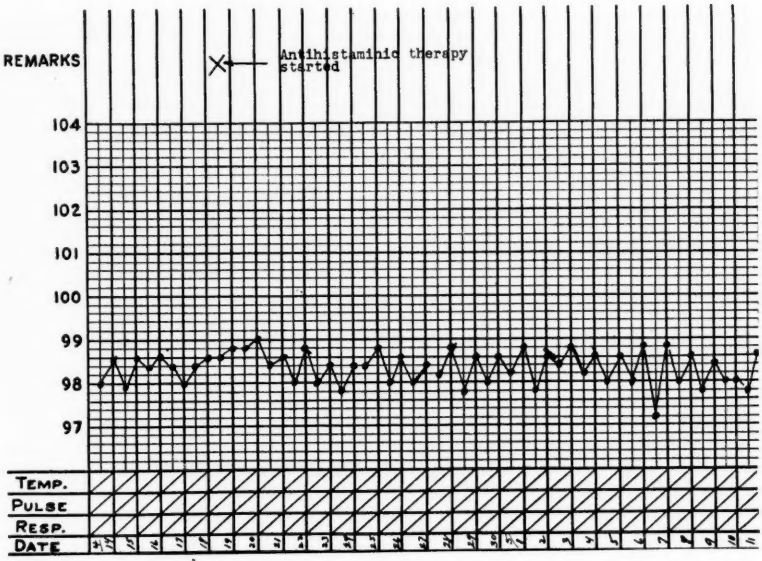

Chart 3. V.L. Temperature record (recorded three times daily) in this case fails to reflect the acute pulmonary episode seen on the roentgenogram.

lymphocytes 46 per cent, mononuclear 3 per cent, eosinophiles 3 per cent, sedimentation rate 21 mm. in sixty minutes (Cutler method) : Sputum was negative for acid-fast bacilli on all examinations, including gastric washings and culture. Basal metabolism rate –9; Wassermann negative; urine normal. X-Ray revealed a minimal lesion in the left pulmonary apex. Temperature, pulse, respiration always remained within normal limits.

Two months after admission an axillary mass suddenly developed near the site of the previous excision. This mass enlarged to the size of an average fist, was tender and obviously inflammatory. It was felt that there had been a recrudescence of the axillary glandular tuberculosis.

The patient was placed on 50 mg. of Pyribenzamine four times daily. This dose was shortly increased to a total of 300 mg. daily, and she was maintained on this schedule. In one week's time the pain in the region had been reduced. After two weeks, there was an obvious decrease in the size of the mass. Pain and tenderness was greatly diminished. By four weeks, the glandular mass had been reduced to the size of a walnut and tenderness was only slight. By the ninth week, the mass was reduced to the size of an almond, and tenderness could only be elicited by pressure. Thereafter, no further change was noted. The Pyribenzamine therapy, 300 mg. daily, was continued for a total of four months. After the ninth week, there was no further change noted in the axilla. The small pulmonary lesion had remained stable throughout the course. Prior to instituting antihistaminic therapy, the Mantoux reaction was plus 2. By the third week it was plus 1 and on the fifth week it was negative and remained so thereafter throughout the remainder of the course of therapy. The patient was discharged August 10, 1948, after seventeen weeks of antihistaminic therapy. No change in the patient's status has been reported since discharge.

Case 5.—G.H., aged twenty-seven, white, female, meat handler, was admitted nine months following the onset of symptoms which had their onset in September, 1947, when she developed a productive cough and debility, accompanied by a weight loss (15 pounds), anorexia, fatigue and night sweats. The physical examination on admission was essentially normal except for evidence of recent loss of weight and signs characteristic of a bilateral pulmonary tuberculosis with cavities in both lungs. Her temperature, pulse and respiration were normal except for an increased respiratory rate up to 28 per minute.

The laboratory findings were as follows: Red blood cells 4,920,000; hemoglobin 88 per cent; white blood cells 17,100; polynuclear neutrophiles 67 per cent; lymphocytes 33 per cent; urine negative; Wassermann negative. Fecal smear—acid-fast bacilli found. Sputum was positive for acid-fast bacilli. Gaffky count was 4, –, 6. Sedimentation rate was 26 mm. in sixty minutes (Cutler method). X-rays revealed bilateral pulmonary tuberculosis with cavitation with greatest degree of involvement in left lung.

Right artificial pneumothorax was successfully instituted (left unsuccessful) and has been maintained without complication. In spite of therapeutic measures, including streptomycin (1 gm. daily, i.e. ½ gm. morning and afternoon for fifty-eight days directed specifically against the tuberculous enteritis), the patient's course continually progressed down-hill with weight loss, irregular temperature elevations to 101—102° F. and evidence of toxicity and tuberculous enteritis.

Six months following admission, she presented an erythema nodosum involving both pretibial areas. Antihistaminic treatment, Benadryl 100 mg. daily for five days, was followed by regression of the lesions within five days, leaving the characteristic residual pigmented areas. The medication was then discontinued. Two weeks following cessation of medication, new nodules appeared and the original nodules reappeared. Antihistaminic therapy, Pyribenzamine 150 mg. daily, was resumed and continued for one month, although all lesions regressed within three days and have not since reappeared.

DISCUSSION

In these thirty cases the clinical response was graded roentgenographically and by temperature changes, character and quantity of sputum; increase in weight, appetite, and feeling of well-being were noted. As seen in Table I, the greatest improvement occurred in patients with tuberculous pneumonia and other acute exudative lesions, which, in our opinion, are a result of hypersensitivity.[7] It is significant that, as the lesions progress in chronicity, the antihistamine drugs become less effective.

Mantoux tests were performed on all patients. Purified Protein Derivative Tuberculin, USP, was used prior to, during, and after administration of the drug. In most instances, a gradual diminution in the intensity of the reactions occurred while antihistaminic drugs were taken. The conversion was not always complete, however, and many individuals occasionally showed a slight positive reaction. The reaction became positive within about four to six weeks after administration of the antihistaminic drug was stopped. Although skin sensitivity is not necessarily a measure of hypersensitivity existing in other tissues, it would appear from our results that clinical improvement roughly parallels suppression of the Mantoux reaction.

Three of the patients who showed striking improvement coincident with

antihistaminic therapy were taken off this medication. Within two to eight weeks, symptoms and signs of the disease recurred and retrogression of the pulmonary lesions were demonstrable by x-rays. Reinstitution of therapy was again followed by striking improvement in all three patients. In these patients, the clinical improvement accompanying the administration of the antihistamines strongly points to the therapeutic effectiveness of these drugs even though improvement lasted only through the administration. The combined administration of antihistaminic drugs to suppress the allergic components of the disease, and streptomycin to suppress the growth of the bacillus, may be very effective treatment. Such combined therapy is under active investigation.

The authors realize that thirty cases are too few to evaluate fully the effectiveness of the antihistamines in human tuberculosis, but feel that such a preliminary report will make possible wider investigation than can be accomplished in any one single clinic.

SUMMARY

The antihistamine drugs have been used with encouraging results in the treatment of human tuberculosis. The best results were obtained in the acute exudative type of tuberculosis. The Mantoux reaction was diminished during antihistamine therapy. Additional clinical investigation is in progress.

The authors acknowledge their indebtedness to John E. Gregory, M.D., for his kind help in these studies.

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IMPORTANT NOTICE!

All members of the College who desire to submit a paper either to be read or to be presented BY TITLE at the Sixth Annual Session to be held at the Jefferson Hotel, St. Louis, January 15, 16, 17, and 18, 1950, are requested to send the manuscript, together with an abstract, to the Chairman of the Program Committee, Dr. Sim Hulsey, 701 Fifth Avenue, Fort Worth, Texas, by September 1, 1949.

NEOHETRAMINE IN THE TREATMENT OF EXPERIMENTAL TUBERCULOSIS

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IN the course of our studies of Neohetramine,[8] it occurred to us that this drug might be beneficial in the treatment of tuberculosis by reducing the allergic reaction of the host to the spread of the tubercle bacillus in the body. This, in effect, might be considered a nonspecific method of desensitization. Specific desensitization by means of graded tuberculin injections, while beneficial in some forms of tuberculosis, is not without danger, and may be used only with great caution.[11] Since Neohetramine has been widely used in large numbers of patients with a minimal incidence of unimportant side effects,[1,4,5,10] it appeared that this drug might afford the benefits of specific desensitization without its danger.

The present communication is a preliminary account of our studies of the effect of Neohetramine on guinea pig tuberculosis.

EXPERIMENTAL

Two consecutive experiments, in which identical methods were used, are reported herein. In each experiment, twenty young tuberculin-negative guinea pigs (400-500 gm.) were infected subcutaneously in the groin with 0.1 mg. of virulent human-type tubercle bacilli (H37RV). All reacted to 1 mg. of Old Tuberculin (Mantoux method) ten days after infection, at which time they were divided into two groups of ten. Each animal in the first group was given 6 mg. of Neohetramine subcutaneously, twice daily, at 9:00 a.m. and 5:00 p.m. The other group was used as untreated controls. All the guinea pigs were weighed and tested with 1 mg. of Old Tuberculin (Mantoux method) at frequent intervals. The only deaths that occurred before the end of the experiment, in which tuberculosis was a major factor, were in the control groups, each of which lost two guinea pigs at times varying from sixty-nine to eighty-four days after infection. Animals were autopsied as soon as possible after death, and all survivors were sacrificed three months after the beginning of treatment. The amount of disease in lungs, liver, spleen, and lymphatic system was estimated. Extensive generalized involvement of an organ is denoted by 4-plus, while minimal involvement, consisting usually of a few discrete lesions, is denoted by 1-plus. Sections of the organs were stained with hematoxylin-eosin and with the Ziehl-Neelsen stain, and the lesions were studied for type of disease and content of acid-fast bacilli.

RESULTS

At no time did the treated guinea pigs show any change in reaction to 1 mg. of Old Tuberculin intracutaneously. The failure may be due to in-

From the Research Laboratories of Nepera Chemical Co., Inc.; Yonkers, N. Y.

TABLE I. AVERAGE GROSS TUBERCULOSIS IN CONTROL AND IN NEOHETRAMINE-TREATED GUINEA PIGS

Exp.	Group	No. g. pigs	Lungs	Liver	Spleen	Glands	Summary
1.	Controls	10	1.2	1.3	2.0	2.6	7.1
	Neohetramine	10	0.6	0.4	0.9	1.5	3.4
2.	Controls	9	1.0	1.4	1.5	2.7	6.6
	Neohetramine	9	0.2	0.3	0.9	1.1	2.5

sufficient concentrations of the drug in the skin.[2,3,6,7] They tolerated the two daily subcutaneous injections of Neohetramine without evidence of local toxicity. Average weight curves for the four groups of animals showed no consistent trend. This weight response, together with the absence of local toxicity, indicates that Neohetramine was well tolerated. Gross findings at autopsy showed that the treated animals had about half the disease found in the controls (Table I).

Microscopic examination of the tissues showed that the H37RV organism, at the infecting dose employed, caused in the control guinea pigs a somewhat slowly progressive disease with moderate fibrosis and caseation. There were small numbers of acid-fast bacilli in the lesions, the cells of which were principally monocytes and epithelioid cells. In the treated animals, however, the disease was decidedly more chronic in character, the tubercles showing more fibrosis, while lymphocytes were prominent among the cells of the lesions. Acid-fast bacilli were rare and often impossible to find in the treated animals. This difference was especially marked in the second experiment.

DISCUSSION

The reasons for the beneficial effects of Neohetramine are not known. A direct antimycobacterial action *in vivo* is improbable because in experiments completed at this time Neohetramine has exhibited no effect on the tubercle bacillus *in vitro*.[9] It is possible, though unlikely, that some metabolic product of Neohetramine may be active. We are inclined to believe that Neohetramine is effective in experimental tuberculosis because of its ability to suppress hypersensitivity reactions. Because of this property, the violent reaction of sensitized tissue to the introduction or the spread of tubercle bacilli may be lessened. If so, tissue and capillary damage are reduced, and the toxemia and pyrexia may be diminished. Under such circumstances, it is conceivable that the natural defenses of the host may be better able to resist the invading microorganisms.

Neohetramine seems best suited for the treatment of tuberculosis which is predominantly exudative in type. Since this is the type of disease in which Streptomycin is most useful, combined therapy should be considered, and for that reason, the effect of both Neohetramine and Streptomycin on guinea pig tuberculosis is under laboratory investigation. If the beneficial effects of Neohetramine in experimental tuberculosis are due to its effect on the hypersensitive state of the animal, the clinical trial of Neohetramine

(Continued on Page 376)

A CLINICAL EVALUATION OF NEOHETRAMINE IN ALLERGIC DISEASES

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THE theory is generally accepted that as a result of an antigen-antibody reaction there is a liberation of histamine, or histamine-like substance, thus causing allergic symptoms in the shock tissues. It is consequently logical to assume that if the histamine liberated could be neutralized or antagonized by a drug that would attach itself to the histamine cell receptors, thus blocking the attachment of released histamine, patients would become symptom-free, or symptoms would be held to a minimum.

Certain phenolic ethers were demonstrated by Fourneau and Bovet[1] in 1933 to have such antihistamine, or histamine antagonistic, properties. However, the toxicity of these first compounds led other investigators to search for drugs less toxic, and several compounds were evolved in France and later in this country. The antihistamine and anti-anaphylactic properties of each of the compounds were studied experimentally in animals. They were shown to prevent histamine-induced contractions of isolated tissue strips and were highly effective in blocking histamine-induced shock and in preventing fatal anaphylactic shock in hypersensitive animals. The degree of activity and the amount of each compound necessary to produce these effects in animals differs sometimes very widely. The activity in animals does not entirely parallel that in human beings.

Gilman,[2] writing on the pharmacology of drugs in allergic conditions, expresses the opinion that the term "antihistaminic" is a poor one to apply to these drugs, as epinephrine is the true physiologic histamine antagonist. He contends that since the "antihistaminic" compounds do not by themselves cause a prominent degree of muscular relaxation or have any effect on peripheral vasculature, we are dealing not with a physiologic histamine antagonist but with a type of blocking agent. The mechanism of action of this blocking agent is similar to that by which atropine can block the effects of acetylcholine or of cholinergic nerve impulses. Gilman proposes the term "histaminolytic" as more appropriate for these compounds.

The histaminolytics have now been used in a great many cases of various allergic diseases, and their therapeutic usefulness as adjuvants is established. Their paradoxical action, however, still needs to be explained. They will relieve only some allergic symptoms and not others, and in some cases, the percentage of relief obtained is small or absent. Gilman explains this by advancing the hypothesis that when histamine is released as a result of the reaction between antigen and antibody, the site of the release is probably directly within the effector cell, and therefore cannot be effectively

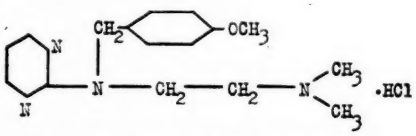
From the Division of Allergy, Department of Medicine, Long Island College Hospital.
Neohetramine was furnished through the courtesy of Nepera Chemical Co., Inc., and is now distributed by Wyeth, Inc.

blocked. The blocking action of a drug can only be effective when histamine comes to the cell by way of the circulation.

The basis of this hypothesis is that histamine is the sole chemical mediator in the antigen-antibody reaction. If the release of histamine is within the effector cell and the histaminolytic cannot block it, how then does effective blocking take place in some instances, and how are some symptoms in an allergic condition ameliorated while others are left untouched? The hypothesis is thus not entirely adequate, and further explanation of the action of the histaminolytics is needed. It was expected that the antihistaminics, by their blocking action of histamine, would serve as a further proof of this theory.

It seems, however, that histamine is not the sole mediator in the reaction, and several investigators have already advanced the possibility of more than one chemical substance being involved. Warren and Dixon,[4] in their antigen tracer studies, proved that the cause of death in guinea pigs from intravenous injection of histamine differs from the cause of death following anaphylactic shock as a result of antigen-antibody reaction. Death from histamine injected intravenously is caused solely by a marked contraction and thickening of the bronchial smooth muscle coat, while the bronchial obstruction in anaphylactic shock, resulting from antigen-antibody reaction, is due to massive edema of the loose bronchial collagenous connective tissue. In view of the above, the original conception of the mechanism in allergy seems to be controversial.

This report is on the clinical evaluation of Neohetramine, one of the histaminolytic drugs developed in this country. Neohetramine is 2-(N-dimethylaminoethyl-N-p methoxybenzyl)-aminopyrimidine monohydrochloride. It is a stable, crystalline, white compound which melts at 173° C., dec., and has the following chemical structure:



$C_{16}H_{22}ON_4 \cdot HCl$ Molecular wt. 322.6

It is highly soluble and relatively stable in aqueous solution. Concentrated solutions are slightly acidic; for example, 1 and 20 per cent solutions exhibit pH values of 5.7 and 4.5, respectively. These solutions may be adjusted to pH 7.0 without precipitation. A 0.2 molal solution of Neohetramine (6.35 per cent at 27° C.) is approximately 45 per cent dissociated and is isotonic with mammalian serum.

Scudi, Reinhald and Dreyer[3] have studied the pharmacologic characteristics of Neohetramine experimentally in animals. In their study of acute toxicity, they found that in mice the oral LD_{50} of Neohetramine is

approximately twice as high as the intraperitoneal LD_{50}, and in guinea pigs, five times as high. In a chronic toxicity study, Neohetramine was administered to 105 weanling rats, either by way of diet, 50 to 200 mg./kg. or subcutaneously, 10 to 20 mg./kg. twice a day for a period of ninety-one days. The animals exhibited normal growth and a complete absence of morphological blood changes or organ pathology.

Neohetramine showed marked activity against the capillary, bronchiolar, local vasodilator and smooth muscle and vasodepression actions of histamine. In actively sensitized guinea pigs, protection was afforded with as little as 1 mg./kg., but larger doses gave no significantly greater protection. In guinea pigs passively sensitized by intraperitoneal injection of 0.5 c.c. of antihorse rabbit serum, good protection was obtained in preanimals with a dose of 5 mg./kg. No protection against local anaphylaxis (Arthus phenomenon) and anaphylaxis in isolated tissue was noted. Five to ten times as much drug was required to protect guinea pigs against anaphylactic as against histamine shock.

In addition to its histamine antagonistic action, Neohetramine exhibits also several other pharmacologic properties. In low concentrations it exerts a mild or no depressant action on smooth muscle, but in high concentration, it induces contractions. It does not potentiate the action of epinephrine and does not alter sympathetic responses. In the eye it produces a transient congestion, accompanied by local anesthesia comparable to procaine. It has slight atropine-like properties, shown by its ability to depress salivary secretion, and it produces some ventricular depression, bradycardia and transient lowering of blood pressure.

CLINICAL STUDY

The present study deals with the use of Neohetramine in 111 cases. This group comprised the following: hay fever, fifty-three cases; vasomotor rhinitis, twenty-two cases; bronchial asthma, twenty-four cases; chronic urticaria, five cases; allergic eczema, six cases; and pruritus, one case. The dose generally used was 50 mg. one to four times a day; though in many cases, 100 mg. three to four times a day was necessary to relieve the symptoms. The amount of the drug given, and the number of doses, had to be adjusted in many individuals according to their individual requirements. In patients benefited by Neohetramine, relief of symptoms or improvement occurred in fifteen minutes to one hour. Several of the patients in this series have taken from 300 to 400 mg. daily for three to four months without any abnormal changes in the blood count, blood chemistry or urine.

Hay Fever.—All hay-fever patients received pre-seasonal hyposensitization, and only those who had not received complete relief of symptoms were given Neohetramine. The response to Neohetramine could be readily evaluated. If relief occurred, it was usually definite within fifteen to thirty

TABLE I. RESULTS OF TREATMENT OF PATIENTS WITH NEOHETRAMINE

Allergic Condition	Number of Cases	Relief	No Relief	Percentage Relieved
Hay fever (ragweed)	41	29	12	70.7
Hay fever (timothy)	7	5	2	71.4
Hay fever (trees)	5	4	1	80.0
Vasomotor rhinitis	22	14	8	63.5
Bronchial asthma	24	10	14	41.7
Allergic Eczema	6	1	5	16.7
Chronic Urticaria	5	3	2	60.0
Pruritus	1	1	0	100.0
Totals	111	67	44	60.4

TABLE II. NEOHETRAMINE (111 CASES)—SIDE REACTIONS (8 CASES—7.2 PER CENT)

Side Reaction	Number of Cases
Drowsiness	2
Dryness of mouth	1
Nausea	1
Bitter taste	1
Tiredness	1
Headache	1
Restlessness	1
Marked nervousness	1
Aggravation of Asthmatic attack	1

minutes and was lasting, making the patient comfortable from several hours to the entire day, frequently on only one or two tablets a day. Symptomatic relief occurred in thirty-eight of fifty-three cases (71.7 per cent).

Vasomotor Rhinitis.—Twenty-two patients with vasomotor rhinitis were treated with Neohetramine. Various forms of therapy, such as elimination of foods and avoidance of inhalants that gave positive skin reactions, vaccine and dust injections, specific hyposensitization and local therapy, were previously given to these patients without relief. When Neohetramine was given in addition, fourteen (63.5 per cent) obtained relief and eight (36.5 per cent) obtained no relief.

Bronchial Asthma.—Of twenty-four patients with bronchial asthma, ten (41.7 per cent) were relieved and fourteen (58.3 per cent) obtained no relief. In some cases the relief obtained was better than with several other antihistaminics, including Benadryl and Pyribenzamine.

Allergic Eczema.—Neohetramine was given to six patients with allergic eczema. One was relieved and five were not. The one who obtained relief was a chronic case in which all forms of local applications, and later Benadryl, gave no relief. Both the itching and the rash completely disappeared after one week's time on 50 mg. of Neohetramine four times a day.

Chronic Urticaria.—In five cases of chronic urticaria three (60 per cent) were relieved and two (40 per cent) were not. One of the patients not relieved by Neohetramine was not relieved by any of the antihistaminics in use now.

Pruritus.—Neohetramine was administered in one case of generalized pruritus and gave complete relief.

SIDE REACTIONS

Of the 111 patients treated with Neohetramine, eight (7.2 per cent) complained of side reactions. Two discontinued the use of the drug—one on account of severe nausea, and the other because of the increase of the asthmatic symptoms one-half hour after the taking of 50 mg. of Neohetramine. Six patients had transitory symptoms: dryness of the mouth; drowsiness at first, which disappeared on further use of the drug; nausea and bitter taste in the mouth; nervousness, headache and restlessness.

SUMMARY

A group of 111 patients with various forms of allergy were treated with Neohetramine. In this group symptomatic relief occurred in sixty-seven patients (60.4 per cent), while forty-four patients (39.6 per cent) obtained either slight or no relief. Side reactions occurred in eight cases (7.2 per cent) of the group of 111 patients.

CONCLUSIONS

Considering the favorable results in 60.4 per cent of the 111 cases, and the very low and mild toxicity, Neohetramine appears to be a valuable drug for use in the symptomatic relief of a variety of allergic diseases.

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AMERICAN SOCIETY OF OPHTHALMOLOGIC AND OTOLARYNGOLOGIC ALLERGY

A joint meeting of the American Society of Ophthalmologic and Otolaryngologic Allergy and the Hansel Foundation was held at the Hotel Sheraton, St. Louis, Missouri, May 30-June 4. On the first day there were guest speakers, a luncheon and round table discussion, and a banquet in the evening. The remaining four days were devoted to intensive, practical instruction in allergy as related to otolaryngology. The course was well attended. An interesting feature was the participation of the registrants in all practical demonstrations, including the various methods of skin testing, cytologic studies, pollen counting and methods of pollen survey. More of this type of instruction in allergy is needed.

SKIN REACTIONS

XVI. Comparison of Antihistaminic Action of Pyribenzamine and Epinephrine Introduced into Human Skin by Electrophoresis

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RECENT emphasis on the use of drugs of the Pyribenzamine type for the inhibition of the whealing and flare reactions in the human skin, has, to a certain extent, led to the neglect of the fact that epinephrine is, if not the most, one of the most powerful antihistaminic drugs, as measured by effect rather than by pharmacodynamic *theory*. In order to aid in the evaluation of the therapeutic possibilities of drugs similar to Pyribenzamine, and of the sympathomimetic amines like epinephrine, it was decided to compare the effect of skin depots of Pyribenzamine hydrochloride and of epinephrine phosphate, administered by electrophoresis, on the production of wheals by histamine superimposed on areas previously treated by Pyribenzamine and by epinephrine.

METHOD

The methods previously developed were utilized.[2,3,5,6] The current density at the positive pole varied between 0.3 and 0.5 milliampere per square centimeter. Canton flannel was saturated with the solutions tested and applied with gentle pressure. As previously described, the electrodes touching the skin were always in contact with aluminum foil. In general, the electrodes were applied to the skin from three to five minutes. The technique developed to study the effect of depots of atropine on the vasodilatation of the skin by mecholyl, was applied with this exception: When epinephrine is introduced into the skin by electrophoresis, in a few minutes the initial irritation due to the introduction of this drug disappears and a clearly blanched area is observed. The type of blanching is illustrated in Figure 1. The blanched area is surrounded by a flare. It is of some interest that this flare resembles the flare produced by histamine itself. As previously observed, with higher concentrations of epinephrine, white psuedopods are observed which are due to the lymphatic escape of the epinephrine into the dermis.[4]

EXPERIMENTS

A typical experiment is illustrated in Figures 1, 2 and 3. Figure 1 represents the effect of 1:10,000 solution of epinephrine phosphate introduced into the forearm electrophoretically with a current density of approximately 0.3 milliampere for 5 minutes. Figure 2 is a photograph of the result of superimposing on, and at right angles to, the area treated

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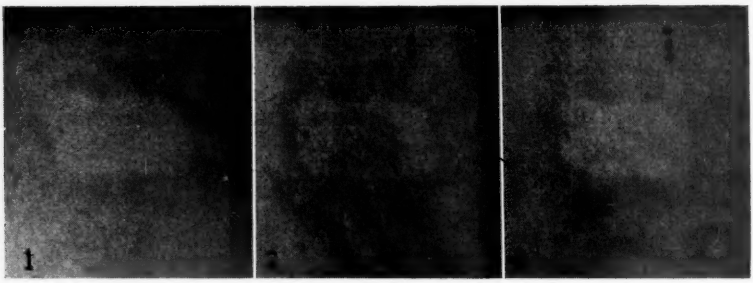

Fig. 1. 1:10,000 epinephrine was introduced into the forearm electrophoretically with a current density of approximately 0.3 ma. for five minutes. Started at 11:00 a.m. There is a flare about the blanched area. Photograph was made at 11:15.

Fig. 2. 1:50,000 histamine introduced with a rectangular electrode, half of which was placed over the site where the epinephrine was introduced. The histamine was electrophoretically introduced at a current density of about 0.3 ma. for two minutes. Area over epinephrine shows slight reddening and slight whealing after five minutes. Entire area is surrounded by flare. Experiment was started at 11:21 and picture was taken at 11:30.

Fig. 3. Photograph taken at 11:45 shows disappearance of histamine reaction and reappearance of blanched area surrounded by flare. This is the "restoration" effect of epinephrine.

with epinephrine, an electrode delivering a 1:50,000 solution of histamine phosphate. This photograph was taken thirty minutes after the epinephrine had been introduced. It illustrates the flare, both around the blanched areas and around those treated only with histamine. In this experiment a fairly distinct elevated wheal was formed over the blanched area. If a stronger solution of epinephrine is used (say, 1:1,000), the whealing is not so marked. However, this histamine reaction is transient. The phenomenon that took place thirty minutes after the introduction of the histamine is illustrated in Figure 3. Although the wheal outside the blanched area persisted, the epinephrine blanching reaction reappeared at the histamine site, with the blanched area almost complete at the original site. This reappearance of the blanching, forty-five minutes after the introduction of histamine, is spectacular. It indicates that even though the blood vessels responded by dilatation and changed permeability to histamine, sufficient epinephrine remained at the site to reassert itself pharmacologically and to restore pharmacologically the antihistamine status of the area treated with epinephrine. It has been shown that histamine *increases* absorption and this phenomenon is unexpected. This "restoration" effect, in all likelihood, is more characteristic of certain of the sympathomimetic amines. Whether it will occur in areas treated with Pyribenzamine is not known.

A striking example of this "restoration effect" was observed when 1:1,000 epinephrine phosphate was observed for three minutes (current density 0.3 milliampere) with 1:1,000 histamine superimposed similarly to the technique depicted in Figure 2. Vasodilatation in the epinephrine-blanched area treated with histamine persisted more than four hours. But as the reddened area disappeared, *the blanching due to the epinephrine*

was restored at the site five hours later.* It is of particular interest that the control part of the histamine wheal often apparently disappeared before that part in the blanched areas when weaker epinephrine solutions were introduced. It is conceivable that under certain circumstances the epinephrine may retard absorption of histamine.

Solutions of 10 per cent and 5 per cent Pyribenzamine hydrochloride produce similar inhibition reactions.[1] Initially, after the introduction of Pyribenzamine hydrochloride by electrophoresis, there is an erythema at the site and small papules form about the pores of the skin. It takes some time for this reaction to disappear, usually about one and one-half hours. As previously shown for atropine and histamine, depots of the drug are formed in the skin. The whealing response to 1:50,000 histamine is essentially inhibited by a depot of 10 per cent Pyribenzamine. In addition, the Pyribenzamine site apparently inhibits the flare. This is not true of epinephrine because the epinephrine itself sets up the flare. It is of interest to compare the epinephrine effect with the Pyribenzamine effect.

A semi-quantitative comparison of the two effects leads to the conclusion that a solution of 1:10,000 epinephrine phosphate is essentially as effective as 1:10 Pyribenzamine hydrochloride with our technique. In addition, there is the "restoration effect" of the epinephrine which occurs after the histamine wheal has disappeared. The epinephrine is about 1,000 times as effective an antihistaminic drug as Pyribenzamine when used electrophoretically. The practical significance of this wide difference will be taken up in the discussion.

DISCUSSION

These experiments were undertaken in an attempt to evaluate the possible advantages to be gained by using Pyribenzamine by electrophoresis or Pyribenzamine in an ointment form in the dermatoses instead of epinephrine. According to these observations, Pyribenzamine has no particular advantage over epinephrine in the dermatoses as far as topical therapy is concerned. It is ordinarily assumed that a histamine-like substance is responsible for many of the lesions and of the symptoms. It appears much more logical to use epinephrine by electrophoresis in suitable concentrations or an epinephrine ointment. Epinephrine ointments at one time found a sphere of usefulness in the dermatoses. However, the emphasis given to the drugs of the Pyribenzamine type has caused the usefulness of epinephrine ointment to be neglected. One of us (H.A.A.), has been studying epinephrine ointments of different concentrations with different vehicles. In view of the systemic effects of epinephrine, it would not be desirable to use high concentrations over extensive areas where there has been a good deal of scratching because

*It seems possible that the histamine action was prolonged over the blanched area due to the vasoconstriction of the epinephrine.

of rapid absorption. However, cautious employment of high concentrations over small areas is feasible. Well-demarcated areas of vasoconstriction are observed over freshly scratched areas. The blanching may persist for hours. The effect of 0.05 per cent epinephrine ointment after one hour is illustrated in Figure 4. These data will form the basis of a subsequent report.

Fig. 4. Blanching produced by 0.05 per cent epinephrine ointment about scratch marks after one hour.

SUMMARY

Epinephrine is one of the most powerful antihistaminic drugs, as measured by effects rather than by the definition in pharmacodynamic theory. In order to evaluate the therapeutic possibilities of drugs similar to Pyribenzamine and of epinephrine in the skin, the effect of skin depots of Pyribenzamine hydrochloride and of epinephrine phosphate, administered by electrophoresis, on the production of wheals by histamine superimposed on areas previously treated by Pyribenzamine and epinephrine, was studied. It was found that, weight for weight, epinephrine was approximately 1,000 times as effective as Pyribenzamine under the conditions of experiment. In addition, a new effect, the "restoration" effect of epinephrine, is described. This restoration effect is the reappearance of epinephrine blanching as long as five hours after the histamine has been administered within the blanched area. It is pointed out that the strong antihistaminic action of epinephrine makes clinical trial of epinephrine ointments in the allergic dermatoses a possibility which should be investigated in detail. The "restoration" effect accounts for the prolonged and effective action of topical therapy with epinephrine, as in aerosol therapy of the lungs.

(Continued on Page 358)

ALLERGY AND THE TONSIL PROBLEM IN CHILDREN

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IT is important that the pediatrician, the allergist and all other medical men who treat children should review the tonsil and adenoid problem in its relation to allergic disease. The tonsils and adenoids in children receive more attention from the medical profession than any other organ. This study is primarily concerned with those patients who had their tonsils and adenoids removed without relief of the original symptoms for which the operation was performed. Re-examination revealed that the tonsils or adenoids "grew back." These children suffered from symptoms indicating irritation or obstruction in the upper or lower respiratory system, usually of a chronic, periodic nature. This investigation was initiated twenty years ago at the Children's Clinic to discover whether tonsils and adenoids "grew back" due to faulty surgical technique or to some other unknown cause. The answer to the problem was very different from that which had been anticipated. This resulted in a reversal of our plan of treatment. The allergic problem was recognized and treated first; then an operation was performed, if still necessary.

The plan was to record the details of the operation, label and preserve all the tonsil specimens removed at operation. When a patient returned complaining of the same symptoms for which he had previously been operated upon, or if, on examination, pieces of lymphoid-tissue were found in the tonsil fossae or postnasal space, the patient's previously removed and preserved tonsils were re-examined. Careful search was made to see if any of the capsule or tonsil was missing that might have served as a focus for a regrowth of tissue. The tonsils were always complete. After a thorough review of these cases, one salient conclusion was definite—*most of these patients had an allergic basis for their symptoms which had not been recognized prior to operation.* The operation had failed because the tonsils had been removed to correct allergic symptoms.

Patients in this series who returned for further treatment usually had the same complaints which had been the indications for the previous operation.

The cardinal symptoms were of two types: (1) The mother stated that the child still had "one cold after another,"[3] usually without fever; that his nose was always "stopped up" and breathing was difficult because he was a mouth breather; that a watery discharge was often present, and that he sniffled and blew his nose frequently, more so early in the morning. (2) Many of these colds were associated with a hacking or clearing of the throat. They often terminated in a deep, hard, dry cough which was more fre-

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quent during the night. Recurrent attacks of croup with or without a respiratory infection were common complaints.

A persistent hacking, tiring cough, often with wheezing, and difficult breathing may accompany the above symptoms. A low-grade fever sometimes persisted for months and had to be differentiated from chronic infections such as tuberculosis, sinusitis and rheumatic fever! A few patients had been told by other physicians that the tonsils and adenoids had "grown back" and should be removed again.

The patients whose tonsils "grew back" revealed that breathing (through the nose) was difficult except when the mouth was open. This was the most common postoperative complaint. The parents frequently asked if the adenoids had been removed! Physical examination of such patients may be normal to inspection. Having the patient blow each side of the nose alternately will often reveal some stuffiness in one or the other nostril due to postnasal edema which cannot be seen by ordinary examination. Acute edema of the anterior turbinates may or may not be present. The fact that the congested nasal passages clear up at times, and the patient breathes normally, then bceomes stuffy at night, indicates that there is no definite constant obstruction, such as would be caused by a large mass of adenoid tissue. The type of stenosis due to large adenoids is usually of the same degree day or night and from day to day, in contrast to the intermittent congestion of the allergic child.

This study is composed of two groups of patients: the author's patients who were known allergic children and who had their tonsils and adenoids removed at the Children's Clinic, and those patients in whom the operation was performed by other physicians elsewhere. The diagnosis of allergy in this latter group was usually made postoperatively. Some observations relating to the children in this series will be presented (Table I). One hundred and thirty-six allergic children had their tonsils and adenoids removed. These children had careful pediatric treatment from birth and were known to be allergic.[2] They also had definite indications for removal of their tonsils and adenoids, which were the same as for nonallergic children. Only four children in this group (3 per cent) had recurrent growth of lymphoid tissue in the tonsil fossae or adenoid area. None of these four children had any previous specific allergic treatment and all were under the age of three years. Both factors may predispose to regrowth of lymphoid tissue.

The tonsillar fossae are not involved in the above syndrome nearly as often as the postnasal spaces. Due to the rather large postnasal adenoid spaces, small amounts of regrowths of lymphoid tissue in this area do not cause noticeable symptoms. If this lymphoid hypertrophy occurs in front of the eustachean tubes, partial deafness may occur. This will improve as the patient's allergic symptoms retrogress. Only a small percentage, as mentioned previously, will have tissue regrowths in the tonsil

TABLE I. TONSILLECTOMY AND ADENOIDECTOMY IN ALLERGIC CHILDREN

Diagnosis Made (Allergy)	No. of Allergic Cases	Diagnosis Known before T.&A.	No. of Cases "Tonsils Grew Back"	Per Cent	No. of Cases Operated upon Twice
Before T.&A.	136	136	4	3	0
After T.&A.	60	10	14	23	6

fossae. It is possible and probable that in some cases incomplete operation may have been the cause, but due to the high degree of training and skill of present-day surgeons this has been a rare occurrence in our observation. The fossae, if seen during an acute infection, may reveal rather prominent reddish swollen lymphoid tissue, often appearing similar to granulation tissue. This is usually located in the lingual area, under the anterior pillar or in the middle of the fossa. These pieces of tissue, when quiescent, will shrink considerably, often resembling scar tissue. They may become infected, the same as any other portion of the throat. A granular or nodular pharynx is often present, with various sized pinhead to pea-sized, roundish, raised areas scattered in the pharynx. The lateral walls are frequently studded with new growths of lymphoid tissue. These findings should always suggest an allergic background. Allergic disease predisposes to hyperplasia of lymphoid tissue especially in the nasopharynx.

Regrowth of tissue in the fossae was noted as early as five months after operation. The operation did not relieve or cure the patient of the symptoms from which he suffered. Surgery of the tonsils and adenoids when performed for the relief of allergic conditions, particularly the various manifestations of hay fever or asthma, usually results in failure. Piness,[10] in 1925, voiced this warning in an article entitled, "Allergy, A Non-Surgical Disease of the Nose and Throat." It is true that there may be a temporary improvement in the asthmatic state. This is possibly due to a shock-like effect of necrotic tissue in the throat or of the anesthetic (Feinberg).[6] Hansel[7] has stated that many allergic patients are considered as having infection, because of the absence of hay fever or asthma at the time of examination or operation. The indications for tonsil and adenoid surgery in the allergic child are the same as those in children without nasal allergy. If the family is frankly told that the operation may improve the child's general health but will not materially influence the allergic symptoms, better future relations will exist between the family and the physician.[5] Evatt has stated that since there are approximately eighty-five deaths a year from tonsillectomy in children under fifteen years, and since this type of surgery is not without danger, it should be regarded as a major operation. In allergic children, with pathologic tonsils, in approximately 50 per cent of these candidates for tonsillectomy, an operation will not be necessary once the allergic symptoms are successfully treated. The tonsil and adenoid tissues will shrink or atrophy. This is a common observation among allergists and pediatricians.

In the second group of sixty children, only ten were suspected of having hay fever or asthma. In this undiagnosed and untreated (for allergy)

group there were fourteen patients (23 per cent) whose "tonsils grew back." Six children (10 per cent) also had their tonsils and/or adenoids operated upon twice, and one child had three operations. All retained their original symptoms. Of the ten children in whom the diagnosis of allergy was suspected prior to operation, only one was improved. None of this group had been treated previously for allergy. In the entire group of 196 cases, forty-three children had been operated upon between the ages of two and three years, and 113 before five years of age. The remaining forty were from five to twelve years of age. The indications for operation were the same for the known allergic group as for any nonallergic child.

COMMENT

The results of this study have indicated that when tonsils and adenoids "grow back," it usually occurs in allergic individuals in whom the diagnosis was not known prior to the operation.

The differential diagnosis between the infectious and allergic cold is important. Cohen and Rudolph[4] in 1931 very ably called attention to this problem. The author[3] had previously commented on the fact that allergy as the cause of frequent colds and chronic coughs in children is overlooked more than any other common disease. Hansel[8] has contributed a simple but very excellent test for diagnosing the allergic cold. Nasal smears will frequently show an excess of eosinophiles, which is pathognomonic of allergic disease. No nasal case should be dismissed as nonallergic until repeated smears have shown very few eosinophiles.

Many observers have noted the relationship between tonsil and adenoid removal and allergy. Peshkin[9] investigated 100 asthmatic children. Seventy-two had had tonsil and adenoid operations; in twenty the tonsils had been removed previously to the onset of the asthma, and in fifty-two they had been removed after the onset of the asthma. In a large percentage of these cases, the operation had been performed for the relief of frequent colds without satisfactory results. Temporary relief of asthma was noted in only one case. Bullen[1] studied 1,000 children who had tonsillectomies and 1,000 controls. He concluded that tonsillectomy does not aid in improving the effects of treatment of respiratory allergy. Hansel sums up this problem by stating that the clinical course of the allergy is much the same whether the tonsils are or are not removed. The Johns Hopkins group[11] studied thirty-four asthmatic children; many with partial deafness. Sixteen (47 per cent) had previous tonsil and adenoid operations, eighteen (53 per cent) did not have operations. All had asthma and lymphoid hyperplasia in the postnasal spaces. All of these patients were allergic children. They were relieved by treatment with a nasopharyngeal radium applicator. In some children who are allergic, a tonsillectomy and adenoidectomy are definitely indicated for other reasons. With careful control of the allergy, the occurrence of complications could be avoided with rea-

sonable safety. It is a common observation that this operation when performed during the pollen season will often aggravate pre-existing pollenosis and may precipitate asthma.

Some contraindications for tonsil and adenoid surgery are suggested: (1) If the patient has a chronic "running nose," seasonal or perennial, which is more or less persistent. This may be present in a child who snores, keeps his mouth open most of the time, especially at night. The history often emphasizes a "stuffy nose" usually worse during the night and upon arising, which clears up during the morning. (2) A history of frequent colds, "one after the other," especially in the winter, and a chronic cough, often worse at night. The cough is often aggravated by fatigue or exercise. The symptoms did not respond to any previous treatment. (3) So-called "chronic sinus infections" with or without migraine type headaches. (4) In children whose tonsils and adenoids "grew back" and who still retain their original symptoms.

SUMMARY AND CONCLUSION

Children whose tonsils and adenoids "grew back" following tonsillectomy and adenoidectomy were found to be those who had undiagnosed and untreated allergic disease. When the allergic symptoms are properly treated in children who require tonsil and adenoid removal, the incidence of regrowth of lymphoid tissue in the tonsil fossae is negligible—3 per cent compared to 27 per cent in undiagnosed, untreated, allergic children. All children in this category should have the benefit of a thorough allergic study. Symptoms of allergic disease are usually not relieved by tonsil and adenoid removal. Early diagnosis and specific thorough treatment is the most effective therapy for symptoms due to allergic disease.

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A STUDY OF THE INCIDENCE OF AIR-BORNE FUNGI IN THE CITY OF RIO DE JANEIRO

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A STUDY of the air-borne molds was made to elucidate local problems concerning allergy.

The complete investigation of the allergy caused by inhalation of fungus spores consists of: (1) qualitative and quantitative identification of the Eumycetes of the surroundings, and the correlation of meteorological and seasonal fluctuations; (2) preparation of respective allergens with the verification of the allergic patients' sensitivity to them. In this paper we shall deal only with the qualitative and quantitative identification stated in item (1).

After reporting the results of two months of air observations in a previous publication,[5] we continued these studies over a period of two years, from September, 1943, to August, 1945.

METHOD

The Petri plate method is preferable to the slide method. Petri plates, 10 cm. in diameter and 2 cm. high, containing Sabouraud's conservation medium,* were exposed horizontally outside a window for a period of fifteen minutes (from 11:45 a.m. to 12:00 noon) at the Hospital São Francisco de Assis, Rio de Janeiro, Brazil.

During the first year (September, 1943, to August, 1944) the plates were exposed once a week, and during the second year (September, 1944, to August, 1945) once every two weeks, following the procedure of Morrow, Prince and Lowe[4].

The plates were left at room temperature for three or more days until the colonies were sufficiently developed for their identification. Those which were not easily identified were transferred to tube slants of the same medium in order to observe and study further. New transfers were sometimes made using different media, and frequently slide cultures were employed. The same numbers were used for the tube cultures as were used for the original colonies on the Petri plates. By marking the reverse of the plate or by making a diagram (processo de decalque), numbers were matched, and colonies could be observed and studied in the tube and plate cultures simultaneously.

In this work we were concerned only with classification to the genus, which is considered of primary importance by Bernstein and Feinberg,[1] that determination of species has less importance in mold allergy. They

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*Glucose	40.0	Agar	30.0
Peptone	10.0	Water	1000.0

TABLE I

Molds	Number of Colonies	Per Cent
Yeasts	476	30.2%
Hormodendrum	261	16.5%
Rhodotorula	259	16.4%
Penicillium	226	14.3%
Aspergillus	127	8.0%
Fusarium	52	3.5%
Miscellaneous:		
Phoma	33	
Trichoderma	21	
Mucor	18	
Stemphylium	13	
Alternaria	10	
Monilia sitophila	9	
Helminthoporium	9	
Rhizopus	8	
Pestalozzia	8	
Acrothecium	8	
Scopulariopsis	6	
Nigrospora	5	
Gloesporium	5	
Chaetomium	3	
Oospora	2	11.1%
Robillardia	2	
Epicoccum	2	
Criptomela	2	
Cephalosporium	2	
Botrytis	1	
Nodulisporium	1	
Fusidium	1	
Periconia	1	
Coniosporium	1	
Septoria	1	
Trachysphaeria	1	
Acrostalagmus	1	
Acrostalagmus	1	

point out that in some instances cross neutralization has occurred even between different genera.

For the classification of fungi we followed Clements and Shear,[2] Olimpio da Fonseca Filho,[3] and Verlande D. Silveira.[6]

RESULTS

A total of 1,852 fungus colonies was found, of which 1,575 were classified, the remaining 277 lacking reproductive structures or other identifying characters.

The six most frequently found were: (1) yeast (Saccharomyces type), (2) Hormodendrum, (3) Rhodotorula, (4) Penicillium, (5) Aspergillus, and (6) Fusarium. Phoma, Trichoderma, Mucor, Stemphylium, Alternaria, Monilia sitophila, Helminthosporium, Rhizopus and others were also found.

Of the total 1,575 colonies, 30.2 per cent were yeasts, 16.5 per cent Hormodendrum, 16.4 per cent Rhodotorula, 14.3 per cent Penicillium, 8.0 per cent Aspergillus and 3.5 per cent Fusarium, the remaining 11.1 per cent including 27 different genera (Table I).

DISCUSSION OF FREQUENT MOLDS

Yeasts.—Whereas yeasts were encountered in large numbers, and represented a variety of forms, seasonal aspects were not apparent, except in the case of the Rhodotorulae.

Rhodotorula.—The Rhodotorulae, which represent 16.4 per cent of the total fungi, were found to have no well-defined seasonal variation, although this genus predominated during the months from May to October (Fig. 1).

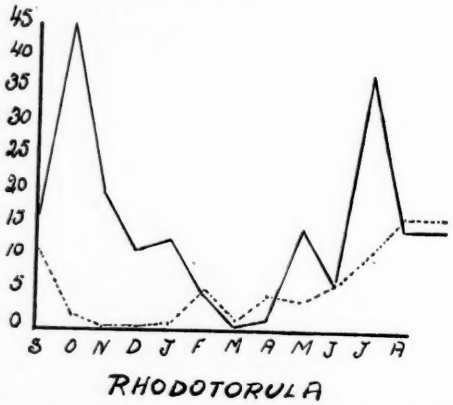

Fig. 1. Solid line represents 1943-1944; dotted line, 1944-1945.

Of the total found during each period during 1943-1944 and 1944-1945, percentages of 70.4 and 78.8, respectively, were identified from May to October. The months of highest incidence were July and October in the 1943-1944 period and August in the 1944-1945 period.

Homodendrum.—This genus showed the clearest seasonal variation, predominating also from May to October, that is, during the end of autumn and winter and beginning of spring in South America (Fig. 2).

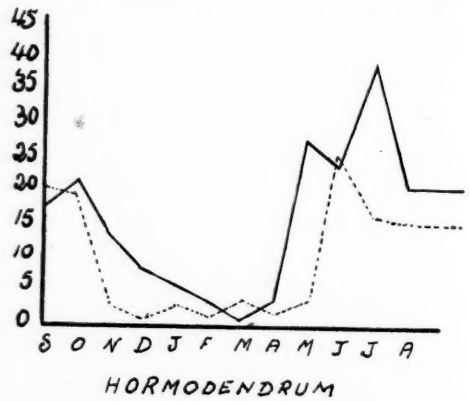

Fig. 2. Dotted line represents 1943-1944; solid line, 1944-1945.

Of the total of the two periods, 83.5 per cent were found during these months. The months of highest incidence were May in the 1943-1944 period and July in the 1944-1945 period. Hormodendrum represents

16.5 per cent of the total fungi and 28.8 per cent of the six more frequently found molds.

Penicillium.—This genus was found with almost the same frequency in all the months of the year, with the exception of December and January

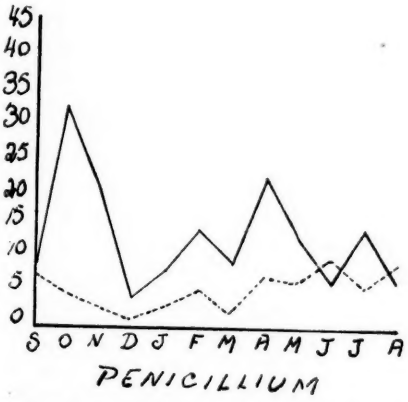

Fig. 3. Solid line represents 1943-1944; dotted line, 1944-1945.

when the number was quite reduced. That is, it had almost the same seasonal variation as Rhodotorula and Hormodendrum, but started earlier and finished later (Fig. 3). The months of highest frequency were October and April in the 1943-1944 period and November and July in the 1944-1945 period. The Penicillium represented 14.3 per cent of the total fungi found during the two periods.

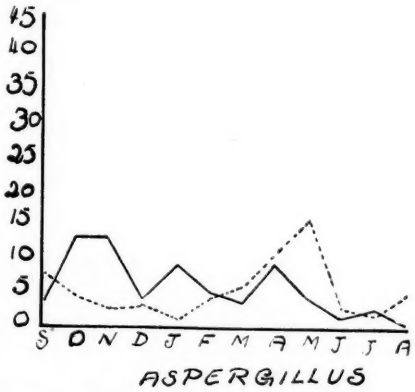

Fig. 4. Solid line represents 1943-1944; dotted line, 1944-1945.

Aspergillus.—There was a lack of seasonal correlation with this genus, since the distribution during the two years was quite uniform (Fig. 4). The lowest incidence was found during June and July in the two periods;

the highest during October and November in the 1943-1944 period and May in the 1944-1945 period. The Aspergilli represented 8.0 per cent of the total.

Fusarium.—Here, also, no seasonal influence was noticed. Fusarium represented 3.5 per cent of the total.

Miscellaneous.—The remaining fungi, which represent 27 different genera form 11.1 per cent of the total, i.e., Phoma, Trichoderma, Mucor, Stemphylium, Alternaria and others, and, although of only occasional occurrence, are noteworthy in that they show a qualitative picture. In regard to the undetermined molds, no seasonal variation was apparent.

The high monthly total counts of all fungi from June to October are a reflection of the corresponding high counts of Hormodendrum, and to a somewhat less degree, of Rhodotorula and Penicillium.

SUMMARY

From the study of the incidence of air-borne fungi in the city of Rio de Janeiro, Brazil, at the Hospital São Francisco de Assis, at first by weekly exposure of Petri plates during the 1943-1944 period and afterwards by semi-monthly exposure during the 1944-1945 period, we concluded that:

1. The most commonly found groups were Yeasts (Saccharomyces type), Hormodendrum, Rhodotorula, Penicillium, Aspergillus and Fusarium, making up 88.9 per cent of total fungi.

2. Seasonal incidence was noted particularly for Hormodendrum and also in the case of Rhodotorula and Penicillium.

3. Highest numbers and seasonal frequency coincide in the months from May to October, that is, from the end of autumn through winter to the beginning of spring in Rio de Janeiro, Brazil, South America.

4. This study is an attempt to aid the allergist of Rio de Janeiro and environs. Further studies of air-borne fungi should be made, and in more detail. These are in prospect. A study of the yeasts would be of interest.

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SINUSITIS, ALLERGY, AND BACTERIAL VACCINE

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THE purpose of this paper is to report certain clinical phenomena and discuss some possible implications and explanations. During more than twenty years the writer has found that hundreds of consecutive unselected cases of both infective and allergic sinusitis have been relieved, benefited, made comfortable, or controlled by an adequate dosage of sensitized mixed vaccine, properly given,* plus some increase of drainage by shrinking drops, used posturally. Concurrently, dependent symptoms such as nasal congestion, postnasal drip, headache, otitis, tonsillitis, laryngitis, bronchitis, asthma, and some skin rashes have cleared up. Mastoiditis has not developed, and operations have not been necessary. In addition to these objective changes, and where they were not demonstrable, the vast majority of patients so treated reported a definite improvement in their symptoms, often after various surgical and medical treatments had given no such relief.

As the late Sir Almroth Wright[15] so clearly argued some ten years ago, the classical method of statistical experimentation is a principle of strictly limited application which cannot always be used for testing the value of therapeutic methods. Fidler makes much the same point in his book, *Whither Medicine, from Dogma to Science.* However, in this case, if one wishes to compare a group of treated cases with a group of untreated cases, he can contrast the condition of several scores or hundreds of people over a period of months and even of years, who have suffered from sinusitis, with a group of individuals whose signs and symptoms become alleviated during a short period of treatment. The fact that the two groups are composed of the same individuals makes the statistical experimentation more accurate, because it rules out a great variety of confusing issues.

The following five case reports have been chosen from hundreds, *as examples only.*

Case 1.—J. P., an eleven-year-old girl, was seen on October 24, 1946, complaining of aching in the frontal region for more than a month and of her eyes giving some discomfort. She had been seen by an eye, ear, nose and throat specialist who exonerated the eyes and sinuses. Sometimes she had a slight earache. Her breath was usually malodorous. Her throat looked irritated, with some mucous discharge. She was given nasal drops and a course of vaccine. On November 1 she was feeling better after two inoculations. She continued to improve steadily under treatment. Seven months after the first visit, her mother reported that she was still doing very well and that the neighbors had noticed that she looked to be in much better health. The bad odor was gone from her breath.

Case 2.—Miss G. E., aged thirty, was seen on April 9, 1946, having been referred by an eye, ear, nose and throat surgeon. She had had chronic nasal blocking and throat soreness as long as she could remember. It was usually worse in winter.

*The exact method of vaccine treatment used is described in detail at the end of this paper.

Another eye, ear, nose and throat specalist had wanted to do skin tests but she had no time. She had considerable pharyngeal dropping, especially in the morning, and frequent headaches. A few skin tests were done. House dust showed 1-plus. About 1/50 c.c. of ordinary cold vaccine produced a similar wheal to that caused by the house dust. She was started on nasal drops and a course of vaccine. Three days later she said she felt better and that her throat felt better. There was continued improvement. On April 25 her voice sounded clearer, and although her throat used to fill up and be uncomfortable, it no longer did. On May 10 she was feeling much better. On some days her head was very clear. On May 31 she felt that her sinuses were much better.

This patient had a slight recurrence the latter part of October and received another course of vaccine. Again she responded very quickly.

Case 3.—M. H., aged twenty-four, stated on August 8, 1942, that for over five years she had been troubled by blocking of the nose, pharyngeal dropping, headaches, tiredness, et cetera, and that she had begun to lose weight. A tonsillectomy five years earlier had given some temporary relief. She was started on a course of nasal drops and vaccine, and felt better five days later. She continued to improve. On September 12 she came in for the sixth dose of vaccine, feeling much better. Her nose was not so blocked and her head not so tight. On October 19 she reported that she still was very well and for all practical purposes seemed cured.

Case 4.—W. W. C., a fifty-year-old man, was seen on January 15, 1943. He had had nasal congestion for two years, following an episode of "flu." He was given nasal drops and only one inoculation of vaccine. He returned on June 17 to report that he had been much better for a month after the January treatment. He improved during June and July under a course of vaccine, until on July 15 he reported that he was having no further trouble with his sinuses.

Case 5.—H. B., a twenty-one-year-old man, seen on October 10, 1947, complained of having a head "cold" almost constantly since he had joined the Air Force in 1945. He had a headache, stuffed nose and pharyngeal dropping. When seen, he seemed to have an acute "cold." He was started on treatment with nasal drops and vaccine. Four days later he said that the headache was gone and his nose was not so "stuffy." On October 23 he felt much better. When he came for his sixth inoculation on November 7, he considered that he was so greatly improved he would not need to return unless the condition reoccurred.

It does not seem that any useful purpose will be served by describing more examples. Some patients developed reoccurrences or new infection. These usually responded more quickly than they had the first time. A few patients did not seem to retain their state of improved immunity (or hyposensitivity) for more than a few weeks. These patients were usually kept comfortable by an inoculation of the optimal dose once a month, until they gradually developed a more prolonged resistance.

Is it possible to suggest a theory to explain both infective and allergic sinusitis which is consistent with the phenomena described? The following comments seem reasonable to the writer as a working hypothesis.

Von Pirquet[11] proposed the term allergy, including bacteria among the many causes. Quoting various workers, he concluded, "Immunization and hypersensitivity therefore can be connected most intimately with one another.

"For this general concept of the *changed capacity to react, I suggest the term allergy.*"

Probably because research workers attempted to separate the sensitivity type of reaction from the immunity type of reaction *for purposes of study,* it became the vogue to forget and ignore Von Pirquet's observation, and to attempt both diagnosis and treatment of the body's reactions on the underlying assumption that this artificial separation also occurred in nature. However, more and more, particularly in the last decade, writers have been recognizing the truth which Von Pirquet saw concerning the fundamental oneness of immunity and sensitivity reactions, and concerning the role of bacteria in allergy.

Burky,[3] Kabat,[9] Wittich,[14] Doerr,[4] Baer,[1] and others have favored this view. Harrington[5] suggests that "anaphylaxis and allergy appear as an embarrassing variant of the same mechanism," and William C. Boyd[2] recently wrote as follows, "Bacterial disease agents seem to act in one or both of two ways: to lead to the formation of protective antibodies or to produce in the host hypersensitivity or allergy to some constituents of the bacterial cell."

Should Von Pirquet's original allergy be subdivided today into immunity reactions, or normalergy, and sensitivity reactions, or exaggergy?

Perhaps all cases of sinusitis are allergic in the Von Pirquet sense, the symptoms and signs in a given case depending upon the proportions which exist between the two types of reaction. The cytologic findings which are usually recorded *could* be interpreted as favoring this viewpoint; increased eosinophilia representing a tendency towards sensitivity reaction, and increased neutrophilia showing more immunological response—both types of cells being usually present to some extent. Hitherto those cases where the immunity response has resulted in marked local symptoms, usually with pus present, or structural changes which can be shown by x-ray, have been called infective sinusitis by the eye, ear, nose and throat surgeons. When local symptoms have been predominantly of the noninflammatory type, the condition has been called allergic sinusitis, and a search usually made for a nonbacterial allergen. Attention has usually been paid to attempts to remove the results of reaction surgically, or to avoid the nonbacterial allergen. Attempts to increase the degree of immunological reaction, or to reduce the sensitivity reaction, have apparently been more successful with some substances than with others.

In pollenosis the nonviable allergen is fairly obvious, a suitable extract can be made, and ascending doses to an optimum size will often so alter the reaction of the body as to relieve the most embarrassing symptoms. Just how is this result accomplished in the body? Why is it not always so accomplished? While we have some theories, we do not know; but our failure to know the "how" is not a reason to refrain from using a treatment which relieves many hay-fever victims!

What about other allergens? Much work has been done with "house dust," another way of saying something or some things which settle as precipitate matter from the air of rooms in which people live. Could the major allergen in house dust be bacteria? The following considerations favor such an idea:

1. Ordinary dust contains many bacteria. Deryl Hart[6] and associates have shown that when healthy masked people occupy an apparently sterile operating room "the air in the operating room is highly contaminated with pathogenic bacteria." Others have corroborated this finding. How much more will the accumulated dust of days in living rooms, whose inhabitants are not masked, contain bacteria? This truth has been studied by Hollaender[7] and associates, Wells and Wells,[13] Thomas,[10] and Murray P. Howard,[8] mostly in connection with infections causing immunity-type reactions in surgical conditions or contagious diseases. Their work has proved that one of the largest elements in household dust is bacteria, especially streptococci and staphylococci.

2. Bacteria represent practically the only allergen which increases in quantity after reaching the body. A few bacteria will very soon multiply in the warm moist linings of the respiratory tract—living allergen, which by the amazing alchemy of the life force is able to use the materials of the host's body to make many thousand times as much allergenic material as was introduced originally!

3. There is evidence to show that dust from such materials as cotton, wool, et cetera, which has "aged" where people live is much more likely to be allergenic than that coming from new materials. This could be because of the bacterial materials which they have accumulated in the course of "aging."

4. In a very few cases where there was a positive skin reaction to "house dust extract" the writer injected about 1/50 c.c. of a mixed (non-sensitized) respiratory vaccine intradermally. This resulted in a wheal very similar to that produced by the dust extract. These few cases are no more than suggestive. Perhaps someone with better facilities will undertake more investigation along these lines. While skin tests do not prove anything in an absolute or dogmatic sense, it would be interesting to know whether a large percentage of those whose skins are sensitive to house dust extract are also similarly sensitive to dead bacteria.†

5. A number of workers who consider they get good results with house dust extracts in treatment frequently add bacterial vaccines to the extract.[12] Moreover, since dry dust contains 20 to 70 per cent organic matter,[8] any extract will of necessity be a form of foreign protein therapy.

†Preceding this paper, one was presented to the American College of Allergists on the work of Doctors Kraft, Mothersill, and Nestman, of Indianapolis, showing that about *30* per cent of their subjects gave immediate urticarial reactions to intradermal injections of bacterial antigens. In personal conversation with two of the authors the present writer learns that their figures were very conservative; had they reported all their *slight* reactions the figure would have been more like *65* per cent.

6. Respiratory allergies seem to be benefited by treatment with sensitized vaccines, properly given, with at least as much success as if treated with house dust extract, even in cases where skin tests are positive to dust extract.

The use of bacterial vaccine is, of course, an attempt to alter the type of reaction of the host—to increase his immunity, or decrease his sensitivity, or both, either specifically or nonspecifically. There have been many contradictory reports as to successes and failures in such attempts.

While there are various references to the use of sensitized vaccines in respiratory infections, the writer has been able to find none to their use in the comparatively large doses he has been using routinely for many years. The sensitizing process is reported by the makers to consist of treating the bacteria with hyperimmune rabbit serum before they are killed. The cells are supposed to take up specific antibodies by adsorption. All serum is removed and the ultimate product is a saline suspension of the "sensitized" bacterial cells.

In the author's cases there has been some evidence of specificity, e.g., a very severe case of sinusitis which improved on a mixed sensitized vaccine continued to give much distress until it was found that pneumococcal infection was involved. Administration of additional pneumococcal antigen cleared up the condition completely. There is also evidence of a nonspecific effect. A few cases of hay fever of the early summer type who came too late to be given grass pollen extract, got such marked benefit from a few "shots" of sensitized mixed vaccine that they went through the summer without symptoms. This is consistent with the evidence given by the late Sir Almroth Wright,[15] who considered that nonspecific immunization is elaborated by the leukocytes.

Possibly some of the benefit obtained from vaccine is of another nonspecific type. If the congestion due to reaction against bacteria is relieved by a reduction of the number of bacteria, because of an increased specific immunity, this would result in a decreased absorption of nonviable allergens, and a consequent lessening of the sensitivity reaction.

Anyone wishing to test the value of this treatment must observe three fundamentals:

1. An efficient antigen must be used. The sensitized product* seems to be efficient.
2. It must be injected subcutaneously—not intramuscularly.
3. The dosage must be sufficient.

Many commercial vaccine manufacturers recommend a maximum dose of 200 million of each organism or perhaps 800 million of all organisms.

Even the makers of the sensitized vaccine* recommend maximum doses

*H. influenzae Serobacterin Vaccine Mixed. Manufactured by Sharp and Dohme Incorporated, Philadelphia, and said to be made from sensitized killed H. influenzae, N. catarrhalis, K. pneumoniae, of each 500 million; D. pneumoniae (types 1, 2, 3, 4, 5, 6, 7, 8, 14), 2,500 million; Staphylococcus aureus and albus, of each 750 million; Streptococcus (hemolytic, group A, types 1, 3, 5, 6, 12, 17, 18, 19), 1,500 million; totaling 7,000 million organisms per c.c.

only of the order of 500 to 2,500 million individual organisms and 7,000 million total count.

For many years the writer has been using maximum doses equivalent to 17,000 million of all organisms. *Many patients do not show improvement until receiving doses of that magnitude!*

Even these doses have sometimes had to be increased slightly to get results. It is no wonder some patients do not acquire sufficient immunity or hyposensitization from doses 1/20 to 1/15 these amounts!

In the present state of our knowledge, one would not dare to dogmatize as to how the body's reaction is changed by this vaccine therapy, but our ignorance is no reason not to secure the benefits. The use of vaccine is not a reason for neglecting any other useful procedures; nor is any other treatment a reason not to use vaccine. For example, polyps and other neoplasms require appropriate treatment, but patients with polyps and those who have had polyps removed will be detoxicated and "feel better" after a course of sensitized vaccine. Pollenosis requires specific desensitization, but vaccine therapy will often remove an added source of irritation. Penicillin inhibits development of many bacteria frequently found in sinusitis, whereas sensitized vaccine increases the effectiveness of the body's immunologic mechanism. The two methods of treatment are complementary.

Drainage from the sinuses is probably aided by using 1 per cent ephedrine in normal saline, or ¼ per cent Neosynephrine, et cetera, by a postural method—but not oftener than twice in twenty-four hours for fear a compensatory congestion may result.

The writer thinks of sensitized vaccine not as a cure-all for sinusitis but as a most useful product. He has learned some principles for its use, which are offered herewith in somewhat dogmatic form:

Product.—H. influenza Serobacterin Vaccine Mixed (No. 4750). Sharp and Dohme.

Interval Between Doses.—As short as three days between smaller doses and five to seven days between larger doses. Doses should not be repeated or increased at intervals of over one month.

Give Subcutaneously.—Not intramuscularly. It is often advisable to divide doses of over 1 c.c., giving half in each of two places.

Local Reactions.—Usually a reddened area about the size of a quarter and some tenderness. If an area of several inches diameter or excessive muscular soreness occurs, it is advisable to repeat the last dose before proceeding to increase dosage.

General Reactions.—These are rare, but a *slight* one is often very beneficial. When chilliness and a feeling for a few hours of taking the "flu" occur, it is well to repeat the last dose or slightly reduce it before proceeding to increase dosage.

In the vast majority of cases one can give the following doses at intervals suggested with very little inconvenience to the patient. These doses can be given to infants and small children safely.

0.2 c.c.; 0.4 c.c.; 0.8 c.c.; 1.2 c.c.; 1.8 c.c.; 2.5 c.c.

In resistant cases repeat the 2.5 c.c. dose several times at intervals of *one to four weeks.* In a few cases, doses of 3 c.c. have to be given before securing an optimal result.

It is naturally a good idea to make sure that the patient's vitamin intake is adequate. It is possibly fair to say that while vitamins will not confer immunity, it is difficult or impossible for the body to develop immunity without an adequate supply of vitamins.

SUMMARY

A sensitized mixed vaccine, injected subcutaneously in sufficient dosage, accompanied by medical drainage, has resulted in relief of symptoms for hundreds of patients with sinusitis treated during a period of over twenty years.

The following considerations may aid in understanding this phenomenon:

1. All sinusitis is possibly allergic in the Von Pirquet sense, and there is not necessarily any sharp line of division between sensitivity and immunity. They may occur together.
2. The great group of persons who are "allergic to dust" may be merely sensitive to bacteria.
3. It is possible that in addition to any specific immunity or hyposensitization, there is also a nonspecific effect which is sufficient to cause the patient to lose his sensitivity to various foreign substances.
4. Increase of specific immunity presumably causes a decrease in the congestion present by reducing the bacterial insult. This should result in reduced absorption of other allergenic material.

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"CEREBRAL EDEMA" DUE TO PHENOBARBITAL SENSITIVITY

Clinical Study of a Case

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THE study of the influence of allergy on the brain was limited indeed until Vaughan,[13] in 1927, demonstrated and reported that migraine in many instances was a manifestation of allergy.

The attention of the allergist and internist has been centered largely on the cutaneous response to drug allergy, chiefly because few such cases reach the autopsy table for gross examination of organs and subsequent microscopic examination of tissues. This is particularly true for phenobarbital sensitivity, as only two cases of phenobarbital eruptions with a fatal outcome[6,9] were reported up to 1941. During that year Winer and Baer[14] reported a third case with a detailed clinical and post-mortem study. Necropsies were obtained in two of these cases, but no mention was made of examination of brain tissue.

Every type of skin manifestation may be evoked by drugs, and the same drug may elicit the most varied responses in the same patient.[12] In fact, drug reactions may simulate any allergic response of any type, affecting any of the organs of the body,[1] and sensitivity may occur by one route and exacerbation by another route.[2]

Not infrequently, headache is one of the symptoms of drug allergy. Kennedy[7] states that the allergic headache has not received nearly enough attention and that many cases of sudden transient cerebral and spinal illnesses can only be explained as being due to a sensitiveness of an allergic character.

The patient described in this report presented cerebral manifestations not frequently observed and multiform cutaneous responses, following exposure to phenobarbital.

CASE REPORT

Miss O. G., a nurse, aged twenty-one years, was admitted to the hospital at 11:30 a.m., February 4, 1946, in a semicomatose condition of two hours' duration. Breathing was markedly irregular. She presented a multiform rash, predominantly morbilliform on the face, neck and extremities, with areas of urticaria and angioneurotic edema.

The history of this illness had to be obtained from her roommate because of the patient's stuporous condition and incoherent speech.

The present illness began approximately five hours before hospitalization, at which time the patient complained of generalized pruritus, rash, and urticaria, with progressive swelling of the eyelids and lips, dull headache and slight fever. She had sought relief from pruritus by means of oatmeal baths without apparent benefit. Further questioning of her friends on the afternoon of admission elicited information that three weeks prior to the present illness the patient took a sulfadiazine tablet (gr. 7.7) four times a day and a phenobarbital (Luminal) tablet (gr. 1½) at bedtime

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for five days, for a "head cold," with complete subsidence of nasal discharge. She continued at her routine duties as a nurse in a contagious disease unit of a large hospital but complained frequently to her roommate of easy fatigue and insomnia at night. Because of further progression of the rash, urticaria, angioneurotic edema and pruritus, hospitalization was advised.

Physical Examination.—The patient was a well-developed and fairly well-nourished young woman in a semicomatose state, acutely ill with morbilliform eruptions of the face, neck, arms and legs, and with scattered scarlatiniform lesions and a few areas of erythema multiform-like lesions most evident on the upper chest, flexor surfaces of the arms, and inner aspects of the thighs. Many urticarial wheals were present on the face, neck and extremities, with marked edema of the lips and eyelids extending over the cheeks.

The forearms, medial surfaces of the thighs, neck and upper portions of the back presented linear excoriations, apparently made by the patient's fingernails on scratching. On admission her temperature was 99.8° F., pulse 76. Respiration was irregular with varying periods of hyperpnea and apnea. The blood pressure was 124/86.

The pharyngeal mucosa was normal in appearance, and indirect laryngoscopy revealed laryngeal structures of normal appearance with no evidence of obstruction. Ascultation and percussion revealed no abnormalities of the thorax, heart or abdomen, with the exception of the irregular breathing previously mentioned. The pelvis was essentially normal.

Many possible clinical diagnoses were entertained at first, namely, measles, rubella, erysipelas, scarlet fever, toxic drug reaction, and drug allergy. The acute infectious diseases were considered because of the skin manifestations, elevation of temperature and a history of recent exposure in a contagious disease unit during her nursing assignment. However, an indirect history of recent phenobarbital ingestion prompted the immediate consideration of barbiturate poisoning.

Picrotoxin 1 c.c. (3.0 mg.) was given intravenously for two doses at five-minute intervals, followed within fifteen minutes by metrazol 3 c.c. (0.3 gm.), but with no discernable improvement.

Four hours later the patient became very irritable, restless and difficult to restrain in bed, with an accentuation of the respiratory irregularity. Phenobarbital sodium (Luminal Sodium) gr. 1½ was given subcutaneously. Within forty minutes the patient was in deep coma with Cheyne-Stokes respiration and an increase in urticarial lesions, followed one hour later by an increase in blood pressure (140/90) and temperature (101.2° F.), with two vomiting attacks.

Phenobarbital sensitivity was then suspected, with probable cerebral disturbance. Ophthalmoscopic examination was requested, which revealed an elevation of the disc, blurring of the margins, dilatation and tortuosity of the vessels and edema of the retina. A spinal puncture was done with the patient in the horizontal position, and the fluid reached a level of 340 mm. in the water manometer. Ten c.c. of macroscopically clear fluid were removed with no evidence of xanthochromia or turbidity. No pellicle was observed on standing.

Laboratory Findings.—Blood: red blood cells, 4,700,000; white blood cells, 4,800; hemoglobin, 13.8. Differential count: polymorphonuclear cells, 68; lymphocytes, 27; eosinophiles, 4; monocytes, 1. Kahn test, negative; Wasserman test, negative. Sedimentation rate, 11 mm. in 60 minutes.

Urine analysis: reaction, acid; specific gravity, 1.024; reducing sugar, negative; albumin, trace.

Spinal fluid: pressure, 340 mm. water (normal 110-130 mm. Ringer's solution, in recumbent position); color, clear; protein, 32 mg. per cent (normal 16-38 mg. per

cent); sugar, 70 mg. per cent (normal 45-80 mg. per cent); cells, 6 lymphocytes and no polymorphonuclear cells (normal 0-5 lymphocytes per cubic mm.); chlorides, NaCl 740 mg. per cent (normal 720-750 mg. per cent).

(The normal findings of the cerebrospinal fluid are from Best and Taylor: Physiological Basis of Medical Practice, 4th ed. Baltimore: Williams and Wilkins Co., 1945.)

Therapy.—Venous infusions of 50 c.c. of 50 per cent glucose were given at one-hour intervals, for two successive injections, in an effort to reduce intracranial pressure. Epinephrine hydrochloride, 1:1000, mimims 6, was given subcutaneously at thirty-minute intervals, for six injections, followed by a copious diuresis. The urticarial lesions began to recede with a concomitant reduction in the edema of the eyelids, lips and face.

A second spinal puncture was performed eight hours after the first, and approximately 12 c.c. of clear fluid was withdrawn. No manometric reading was made, but the fluid spurted for a distance of 5 to 6 inches, indicating that it was still under pressure. The characteristics macroscopically were the same as those of the first specimen. The patient became less comatose and within one hour and a half complained of a dull headache at the base of the skull, which disappeared approximately four hours later.

Daily infusions of hypertonic glucose (500 c.c., 10 per cent) were given for four days, and favorable results followed this therapeutic regime, with marked clinical improvement within forty-eight hours. She became relatively lucid and gave the information that during the night prior to hospitalization she had ingested a phenobarbital tablet (Luminal) gr. 1½ at bedtime because of insomnia and fatigue. During this interval she denied taking any other medication. A past history was obtained from the patient for the first time during this period of questioning.

Past History.—She had frequent colds three to four times a year, not seasonally, and a sore throat three to four times a year. She was a known streptococci carrier (Beta hemolytic type) but usually responded to sulfonamide therapy. She denied hay fever, bronchial asthma, eczema and sinusitis. Her surgical history was negative. She had had immunizations for smallpox, diphtheria, and whooping cough, with no known sequelae.

Her allergic history revealed frequent abdominal bloating with cramps, a scarlatiniform rash and urticaria, followed by a headache, after eating cranberries and strawberries. Her family history was negative for asthma, hay fever, migraine, tuberculosis, allergic rhinitis, sinusitis, eczema and urticaria.

The clinical course of the patient showed satisfactory progress with the aforementioned therapy, and on the fifth hospital day she was well oriented, sitting in a chair, with a normal temperature, pulse, respiration and blood pressure (120/82). Food was given by mouth without postprandial distress, and a hospital discharge was considered. It was suggested at this time, however, that cutaneous tests be made with phenobarbital, realizing fully that only in exceptional instances and only occasionally in true urticarial drug eruptions will the appropriate skin test prove valuable.[11] The test was performed and revealed a 1-plus to 2-plus reaction (wheal 0.5 cm., with moderate areola). Similar tests were made later with Seconal Sodium and Sodium Amytal with no reaction.

One hour after the test with phenobarbital, the patient was semicomatose, with irregular respiration and with alternate periods of hyperpnea and apnea. The temperature rose to 99.8° F., and the skin manifestations simulated those of the day of admission.

A venoclysis of hypertonic glucose with epinephrine was employed. The cerebral and respiratory symptoms disappeared within six hours. A slight pigmentation of the skin in the areas of previous urticaria persisted for days.

In our effort to procure an additional confirmatory diagnostic aid, we employed the passive transfer test six days after the direct skin test, and the response was similar to the cutaneous test, though with slightly less erythema. Occasionally a passive transfer is temporarily positive in drug allergies, as shown in a case of Criep[3] and of Zeller.[15].

The remainder of the hospital stay was uneventful, and the patient was discharged symptom-free on the fourteenth hospital day, with the advice to avoid drugs containing phenobarbital. Such avoidance has led to freedom from symptoms.

SUMMARY AND CONCLUSIONS

1. A case of multiform cutaneous lesions with fever, urticaria, angioneurotic edema, coma and marked increase in cerebrospinal fluid pressure after phenobarbital exposure, is reported for the first time.

2. The antigen in this case is most likely a hapten,[8] a drug-protein combination resulting from a conjugation with one of the plasma or tissue protein fractions. It appears, however, that the chemical substance itself may react with the antibodies once they are formed.[10]

3. Drug sensitivity, as represented by this case, often develops in patients who have taken a drug without reaction for months or even years, yet, subsequently, experience a severe, almost fatal reaction following the exhibition of an amount much smaller than the recommended therapeutic dose.

4. A high index of suspicion of drug sensitivity should exist in any atypical condition where there is a history of exposure to the drug. Usually these drugs are for headache, pain, insomnia or constipation.

5. Next to aspirin, the group of barbituric acid compounds is probably the most widely employed of the drugs in general use.[5] This is particularly true for persons engaged in medicine and allied fields, because of frequent fatigue, insomnia and the ready availability of the drug.

6. Many allergic conditions, because of reversibility, may not be diagnosed if the history, signs and symptoms are not properly evaluated early; and although positive skin tests will not often be successful, there should be no abandonment of all forms of skin testing in suspected drug allergy.[4]

7. The clinical signs and symptoms in the case reported, with the ophthalmoscopic findings and marked increase in cerebrospinal fluid pressure, are indicative of cerebral edema with increased intracranial pressure. These recurred with a similar clinical course after re-exposure to the suspected drug. These findings, I believe, substantiate the diagnosis.

I am grateful to the Departments of Ophthalmology and Otolaryngology, Provident Hospital, for assistance in the work-up of this case. I also wish to acknowledge particularly the co-operation of Dr. J. M. Richardson in the ophthalmoscopic examinations and Dr. Harold Wagner, Billings Hospital, for suggested therapy.

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BACTERIAL ALLERGY

An Extreme Hypersensitization Commonly Found in Chronic Brucellosis

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IT is well known that some invading bacteria have a greater capacity for producing a hypersensitive state than others. For example, the tubercle bacillus produces in many patients a marked hypersensitiveness to its specific proteins. This is the basis of the local tuberculin reaction of the cutaneous diagnostic tests of Von Pirquet, Wolff-Eisner, Moro, Mantoux and Vollmer, and of the focal and general reactions following subcutaneous injection of tuberculin which have made tuberculin therapy in pulmonary tuberculosis difficult and hazardous. The causative organisms of rheumatic fever and perhaps rheumatoid arthritis are thought by many[12] to be relatively benign unless and until the host begins to produce a hypersensitive collagenous reaction in the connective tissues, usually some weeks or months after the onset and subsidence of the acute invasion.

Less well known is the fact that extreme sensitization to substances of Brucella organisms occurs very readily in brucellosis (undulant fever) and that this sensitization is a common cause of chronic illness.[13,14] At least 10 per cent of the general population have become sensitized to Brucella, as determined by skin-testing surveys.[1,2,9,11] This figure is much lower in eastern urban areas where pasteurization of the milk supply has been practiced for many years. It is very much higher in areas where raw milk has been customarily consumed.[7] It is also higher by 50 per cent in groups of patients who present diagnostic problems associated with chronic illness, debility and rheumatoid and psychosomatic symptoms.[4]

When a patient who is chronically or recurrently ill presents any clinical and laboratory evidences of Brucella infection, such as fever hyperidrosis, typical blood counts and positive blood agglutination, opsonic, or complement fixation reactions, a diagnosis of chronic brucellosis is usually made. In our experience with about 500 cases of chronic brucellosis, the incidence of detectable skin sensitivity to specific Brucella substances has been 98 per cent. Other writers[4,16,17] state that the skin tests may be negative in 5 to 10 per cent of cases of chronic brucellosis. The diagnosis is often so difficult to prove that it seems hazardous to diagnose chronic brucellosis in the face of negative skin tests unless a positive Brucella culture or other strong evidence is obtained. It is well known that many persons who are apparently perfectly healthy also react to Brucella substances with positive skin tests,[18,20] so a diagnosis on this basis alone is often not tenable.

The extreme degrees of hypersensitization (Fig. 1) to Brucella, consisting of complete tissue intolerance to ordinary doses of Brucella proteins,

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resulting in necrosis of the skin, indolent ulcer formation and permanent scars, have been found to occur, in our experience, only among patients with chronic brucellosis. These reactions differ markedly from the ordinary large positive skin reaction, consisting of temporary indurated erythema

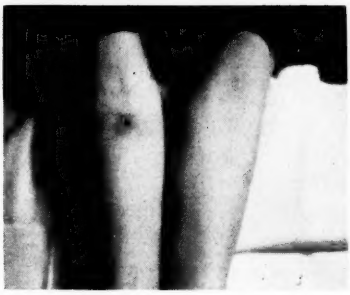

Fig. 1. The left arm presents a reaction to brucellergen which was positive but was considered inconclusive. Five days later a skin test with undiluted vaccine was given on the right arm. The photograph shows the resulting necrosis as it appeared three weeks later.

of a few weeks' or months' duration and commonly called 3 plus or 4 plus, which may be encountered in veterinarians and other cattle-and-pig handlers who are not sick. If Brucella vaccine is injected subcutaneously into the extremely hypersensitized patients with chronic brucellosis, it produces liquefaction necrosis and sterile abscesses at the sites of injection (Fig. 2) as in the Arthus phenomenon. Patients afflicted with such a degree of hypersensitiveness to Brucella will react in this manner quite uniformly to any ordinary doses of vaccine or Brucella skin testing materials. We have never seen a patient with such a reaction who does not have chronic and recurrent complaints which are incompatible with good health and which are typical of chronic brucellosis. The incidence of the extreme type of brucellar hypersensitization has varied between 16 per cent and 25 per cent in groups of 100 patients with chronic brucellosis, according to our records. If, in the future, as a result of improved methods of diagnosis, chronic brucellosis should be proved to be more common, this incidence of hypersensitization will prove to be proportionately too high. On the basis of these figures, extreme brucellar hypersensitiveness is a serious obstacle to the successful treatment[14] of one patient out of every five who are recognized as having chronic brucellosis.

In practice, extreme hypersensitization assumes an even greater importance in treatment than is indicated by the above figures. The methods of vaccine therapy which have usually been advised for chronic brucellosis have called for large doses equivalent to several hundred thousand or several million killed bacteria. Apparently the objective has been to shock or jolt the patient into resisting the disease. Unfortunately, this procedure,

when done with Brucella substances, often increases the patient's sensitization, instead of, or in addition to, immunizing him. As a result of such sensitizing treatment, the patient remains ill, sometimes even worse than before treatment, in spite of the presence of a reassuring titer of opsonins and agglutinins in his blood stream. If large doses of vaccine are continued and are given too frequently or too infrequently, many patients show an increasing intolerance to the vaccine, both locally and generally, even though no excessive hypersensitivity to Brucella was present at the time of the diagnostic skin test (Fig. 3). Such a patient is becoming sensitized and vaccine therapy will have to be discontinued, usually without a cure or even much improvement. In our experience with large doses of unmodified Brucella vaccines, only 60 per cent of the patients improved,[14] a percentage too low to justify such unpleasant treatment. Consequently, Brucella vaccine therapy has been abandoned by many physicians who have had similar experience.

The following cases illustrate the above points:

Case 1.—Mrs. A. B., aged forty-five, had suffered from chronic brucellosis which went undiagnosed for at least five, probably ten years. Her chief symptoms had been lack of energy, myalgia, headaches, severe eyestrain without refractive error, eczema, twitching of the eyelid, occasional tachycardia, and severe constipation. Extensive treatment for allergy resulted in only slight success. There was no eosinophilia. Her Brucella agglutination reaction was negative, but her phagocytic index number (Foshay) was 65 per cent. After the blood was taken for these tests she was given 0.10 c.c. of Brucellergen 1:12,000 intracutaneously on the right forearm. This resulted in a necrotic ulceration, 1 cm. in diameter, at the site of injection. At the same time a herpetiform lesion appeared on the right forefinger and the patient was seized by a severe lassitude and somnolence. In order to determine the specificity of this necrotic reaction, the patient's allergist skin-tested her to nucleic acid, phenol and salt, which are the only ingredients in Brucellergen other than the specific Brucella proteins. These tests were negative, proving that the Brucella proteins were responsible for the reaction. Ten subcutaneous injections of oxidized Brucella vaccine in doses representing material of from two million down to 0.4 of one bacterium, all produced persistent red nodules topped by slight superficial necrosis of the epidermis. During this time there was no clinical improvement and the eczema became worse. After one month without vaccine, the patient was given a dose of 0.05 c.c. of a 10^{-12} dilution of the vaccine intravenously. Theoretically, this represented the protein from 0.00002 of one Brucella bacterium. It put the patient to bed for one and a half days with headache, fever of 2 degrees and inability to sleep. Four more intravenous doses were tolerated with much less general reaction, but when intramuscular doses of the same size were attempted again, necrosis of the needle tracts recurred and desquamation continued at these sites for three months.

Case 2.—H. N. H., a nurse, aged forty-six, had had, from 1934 to 1938, encephalitis, optic neuritis, cholecystitis, and osteomyelitis of the upper jaw, resulting in a permanent draining fistula. In 1938 the case was diagnosed as brucellosis by Dr. W. H. Gaub, and the patient was given treatment by intracutaneous injections of Brucella vaccine. Each injection resulted in a large slough. Four years later she presented herself with seven smooth depressed scars in her skin, 2.5 to 9 cm. in

diameter. She had been disabled for six years. After failing to respond to two other kinds of vaccine, she was rehabilitated by extremely careful desensitization with Foshay's oxidized Brucella vaccine. She was never cured. Her sister and her sister's daughter also had chronic brucellar osteitis and hypersensitization.

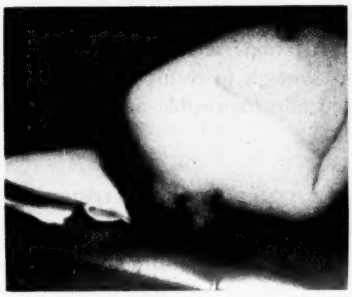

Fig. 2.

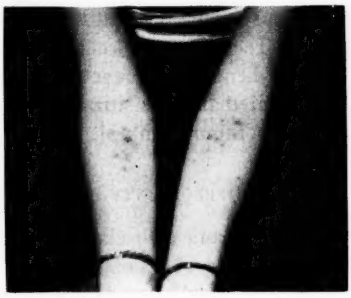

Fig. 3.

Fig. 2. The patient's left upper arm presents sterile abscesses and depressed scars of healed subcutaneous necrosis caused by each of six doses of commercial Brucella vaccine.

Fig. 3. Some of the thirty red, indurated sites of intracutaneous and subcutaneous injections of commercial Brucella vaccine presented by a patient with chronic brucellosis of three years' duration. Fifteen sterile abscesses and granulomas were excised from this patient before desensitization could be started.

Case 3.—A. V. S., a physician, aged sixty-nine, had an insidious onset of a gradually disabling illness which he correctly diagnosed as undulant fever. He had been drinking and prescribing raw milk. His agglutination test was negative. He was given 0.10 c.c. of Brucellergen 1:12,000 intracutaneously. A 4-plus reaction with slight central softening and premature desquamation resulted. He was given 0.25 c.c. (500 million killed bacteria) of a commercial Brucella abortus and Brucella suis vaccine, as advised on the leaflet accompanying the vaccine. The dose was repeated once and then doubled. The patient experienced such an exacerbation of aching, depression, and somnolence after each injection that this vaccine was discontinued. He developed a painful glossitis, multiple ulcerations of the pharynx, diplopia, marked torpidity, occasional short deleria, loss of memory, complete aversion to food and generalized stiffness of muscles and joints. A sterile abscess was formed at each of the three sites of vaccine injection. The abscesses were evacuated of liquefied fat and pus which, on culture, were found to be sterile. These necrotic reactions appeared very slowly over a period of two to six months. The lesions did not heal for seven months. Meanwhile, every possible attempt to desensitize the patient or to improve his condition resulted in failure. He reacted generally to an intravenous injection of the protein of only four bacteria. He showed no improvement until after the last abscess had entirely healed, after he had spent seven months in bed. He was disabled for one year, and he has never fully recovered.

Case 4.—F. J., aged thirty-four, presented herself with two scars from necrotic skin reactions to Brucella substances given five years and three years previously. In addition, she had large scars from sterile abscesses on both upper arms and on one thigh and one persistent nodular induration which had been present for three years in the subcutaneous areolar tissues. These resulted from commercial vaccine which had been started within two days after the second skin test was given. This unfortunate experience with vaccine could have been avoided if the significance

of the first necrotic skin test had been fully appreciated. This patient, like many other such hypersensitive cases, has a lesion in her spine, which is typical of brucellar spondylitis.[5,15,19,25]

The cases cited above are representative of at least fifty such cases seen by us during the past ten years. They illustrate the objective manifestations of extreme brucellar hypersensitization; and that sensitivity increases whenever the reaction is severe enough to result in tissue breakdown, and that desensitization is practically impossible as long as such necrosis continues unhealed.

THE SPECIFICITY OF HYPERSENSITIVENESS IN BRUCELLOSIS

Many patients with chronic brucellosis have had symptoms which have led to a diagnosis of allergy, as in Case 1 above. Nasal catarrh, allergic "sinusitis," frequent sore throat, persistent cough, migrainoid headache, easy fatigability, skin eruptions and myriad gastrointestinal disorders are all common in chronic brucellosis. Patients with these symptoms usually do not respond to treatment for food and pollen allergies, as in Case 1 and many others. The question arises, are these symptoms due to active invasion of the involved tissues by living Brucella organisms or are they merely local tissue manifestations of a generalized hypersensitive state due to foci of brucellar antigens elsewhere in the body, or are they due to extrinsic allergens to which the body reacts excessively because it is already fighting a chronic infectious disease and is therefore in a nonspecifically hypersensitized phase? Fondé[6] seems to conceive of a combination of the last two explanations. Certainly our experience enables us to agree that hyposensitizing patients with chronic brucellosis by means of dilute Brucella vaccine brings about more improvement of all their symptoms than can be expected from any other therapy.

Although acute brucellosis is accompanied by invasion of practically all body tissues[21] by Brucella organisms with the formation of granulomata,[22,24] and although we know that most strains of Brucella prefer an intracellular existence,[3,10] we lack cultural evidence that the respiratory and gastrointestinal symptoms of chronic brucellosis are due to the presence of living Brucella organisms in the reacting tissues. Whether residual antigen may continue to remain in the tissue cells after the microorganism has died is not known. The clinical picture in many cases of chronic brucellosis suggests that hypersensitive reactions do take place in many tissues of the body where active infection cannot objectively be proved.

As for extrinsic allergens, we have seen cases of brucellosis in which they were responsible for important complications. But we have seen more cases in which the patients were tested and found insensitive to extrinsic allergens. Case 4, for example, has been studied extensively in many of the diagnostic clinics of this country by various methods, and no extrinsic allergen has ever been detected. Yet this patient is the most severely

sensitized person, as far as Brucella is concerned, we have encountered. It is chiefly the evidence growing out of the quantitative study of Brucella hypersensitization that inclines us to believe that hypersensitiveness in chronic brucellosis is highly and chiefly specific.

QUANTITATIVE STUDIES OF HYPERSENSITIVITY

Our good results in treating those patients with chronic brucellosis who are not extremely hypersensitive with oxidized[8,14] Brucella vaccine led us to attempt to hyposensitize the group of extremely hypersensitized patients also. The first task was to find out how small the dose of vaccine must be in order to be tolerated by the most hypersensitive patients. The vaccine was diluted progressively as the need arose until 12 decimal dilutions were reached. Since this approached the theoretical limit of dilution for protein molecules, it seemed unreasonable to dilute further. However, further dilution was demanded by the persistence of tissue intolerance at this level of dosage. Apparently flying in the face of theory, we diluted to 20 decimal dilutions: that is, we took a vaccine suspension containing about 400,000,000 bacteria per c.c., killed and oxidized, and diluted it with physiological saline by 10^{20}. Phenol, 0.2 per cent, was added to the diluent as a preservative. Control injections of the diluent and the phenolized diluent which were frequently given to our patients elicited no reactions. The dilutions were frequently cultured, and none were found to be contaminated. Theoretically, the ninth dilution would be the last one to contain the amount of protein in one bacterium. Protein molecules would be expected to disappear at about the fourteenth dilution. In the twentieth dilution it is hard to see how any of the original substance could still be present. Nevertheless, there were more than a score of patients who could not tolerate doses of the twentieth dilution without objective local reactions lasting for more than two weeks, and subjective general reactions which were too uniform to be doubted.

Physical chemists were consulted, and it was agreed that Brucella proteins were probably being adsorbed on syringes, needles, bottles, et cetera, in spite of meticulous cleaning methods. It was assumed that the adsorbed proteins from strong dilutions contaminated the weaker dilutions in unpredictable quantities, thus giving rise to the hypersensitive reactions in the hypersensitized patients. We know two physicians who, unaware of this error, diluted Brucella vaccine empirically and progressively until they were using 120 and 750 decimal dilutions respectively! Because they were not removing all of the vaccine from their syringes and needles in their cleaning processes, they continued to get objective reactions to these infinite dilutions, which were indefensible on theoretical and mathematical grounds. Their clinical results were also quite good, though inconsistent, because minute traces of vaccine were actually present in unknown doses of molecular size.

To eliminate the error of adsorption,[26] new dilutions were made up using

all new bottles, new rubber stoppers, and new needles. After each use, syringes were soaked in concentrated sulfuric acid-dichromate cleaning solution over night. Needles were cleansed with detergent before and after soaking one half hour in a 1 per cent solution of sodium hydroxide

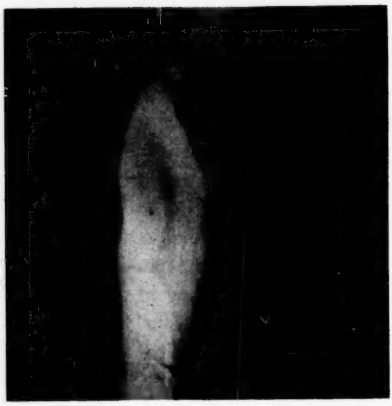

Fig. 4. Forearm of a patient with chronic brucellosis showing hypersensitivity reactions. The old scar in the central area resulted from a diagnostic skin test given four years before. The upper medial reaction resulted from a 10^{-8} dilution of Brucella vaccine given forty-eight hours before. Below it is a smaller reaction to a 10^{-10} dilution. Injections of a 10^{-20} dilution and a control were given equidistantly below these but the sites are scarcely visible after forty-eight hours.

in 75 per cent alcohol. An attempt was made to eliminate every possibility of contamination with unmeasured amounts of Brucella vaccine. Control injections proved that there was no contamination from bottles, stoppers, diluent, phenol, syringes, needles, the alcohol for skin sterilizing, or the cotton applicators. But when the twentieth dilution was injected into Case 4, cited above, she reacted with cutaneous and subcutaneous nodules which remained palpable for three weeks. At the end of this time, two of these nodules were excised and sent to a pathologist for examination. His report was: "Low grade, chronic inflammation in subcutaneous tissue. In the corium is a central area showing an increase in the amount of fibrous connective tissue moderately infiltrated with small round cells."

Figure 4 shows the forearm of another hypersensitive patient who reacted to these extreme dilutions of Brucella vaccine. The upper central portion shows the healed scar of a necrotic reaction to a skin test given four years ago. Medial to it are three intracutaneous injection sites in a vertical line. The lowest one is negative, and is therefore scarcely visible. It was the site of injection of 0.05 c.c. of the twentieth decimal dilution of oxidized Brucella suis vaccine. The middle site, just over the vein, shows the slightly swollen, indurated erythema due to 0.05 c.c. of the nineteenth

dilution. The upper site was caused by 0.05 c.c. of the eighteenth dilution and is proportionately larger. The reactions did not disappear for one month or more. There was necrosis of the superficial layers of skin around the needle tract of the eighteenth dilution. The reaction to a control injection of the diluent given below these three sites was negative. The photograph was taken forty-eight hours after the injections were made.

SUMMARY AND CONCLUSIONS

It is clear that our quantitative study of brucellar hypersensitization is far from complete. Phenomena have been observed for which we now have no theoretical explanation. The clinical significance of our findings to date, however, can be summarized as follows:

1. Regardless of the ultimate explanation of the activity of the extreme dilutions of Brucella vaccine, the fact appears established that some patients with chronic brucellosis develop very severe degrees of hypersensitization to Brucella vaccine.

2. Tissue necrosis resulting from hypersensitive reaction seems to increase hypersensitization and to prevent hyposensitizing procedures until after healing of the necrotic area is complete.

3. There are strong suggestions that much of so-called chronic brucellosis is more accurately conceived as an intrinsic brucellar hypersensitiveness rather than as an active propagation or progressive invasion of living Brucella organisms.

4. Hyposensitization brings about improvement in chronic brucellosis and in the symptoms of hypersensitiveness associated with this condition.

5. There are, however, some patients with such severe degrees of hypersensitization to Brucella vaccine that no dose has yet been found small enough which they can tolerate well. This fact requires further study, both theoretically and practically.

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SKIN REACTIONS XVI

(Continued from Page 328)

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THE DIAGNOSIS AND TREATMENT OF PERENNIAL ALLERGIC CORYZA

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PERENNIAL allergic coryza is one of the most common upper respiratory tract conditions and, perhaps, the most neglected. Its successful treatment is entirely dependent upon integrating several therapeutic measures, not any one of which is sufficient to produce prolonged and sustained improvement. For the purpose of this paper, perennial allergic coryza is synonymous with vasomotor rhinitis, allergic rhinitis, nasal asthma, atopic coryza, nonseasonal hay fever, hyperesthetic rhinitis, et cetera. The term perennial allergic coryza completely describes the continued nonseasonal time element, the etiologic nature, and the anatomical structures of the symptom complex involved.

CLINICAL DIAGNOSIS

Statistics.—Data recorded from a study of 180 cases of perennial allergic coryza, obtained from private practice over a period of two years, are presented. In our series, the syndrome affected females more often than males—100 (55.6 per cent) against eighty (44.4 per cent). At the time at which the patients presented themselves for treatment, 124 (68.8 per cent) were under forty years of age while fifty-six patients (31.2 per cent) were over forty years. Many had had their symptoms for as long as ten to twenty years. Undoubtedly, if the age of onset was considered, many of the older age group would be classified in the younger age brackets. According to our records, the age incidence was: in the first decade, twenty cases; in the second, thirty-six; in the third, twenty-eight; in the fourth, forty; in the fifth, twenty-eight; in the sixth, twenty-one; in the seventh, seven. A positive family history of allergy was obtained in 114 cases (63.3 per cent), while sixty-six patients (36.7 per cent) gave a negative history of any allergic manifestation appearing in the family. In the former group, thirty-eight patients (21 per cent) gave a bilateral family history of allergy, while seventy-six patients (42 per cent) presented a positive unilateral history. Careful and patient interrogation was required to elicit this information, because oftentimes either the patient or the parent is unaware of an allergic syndrome existing in the family tree or, perhaps, the parent is reluctant to make the admission, thinking that it is personally incriminating.

Syndrome Combinations.—Other allergic manifestations are often associated with perennial allergic coryza. It very frequently occurs with bronchial asthma and pollinosis, and less often with colitis, migraine,

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TABLE I. INCIDENCE OF ALLERGIC SYNDROME COMBINATIONS

(The Predominant Syndrome is Listed First)

Perennial allergic coryza	61 cases	(33.8%)
Perennial allergic coryza and bronchial asthma	36 cases	(20%)
Bronchial asthma and perennial allergic coryza	20 cases	(11.1%)
Perennial allergic coryza, pollinosis, and bronchial asthma	27 cases	(15%)
Bronchial asthma, pollinosis, and perennial allergic coryza	14 cases	(7.7%)
Perennial allergic coryza and pollinosis	10 cases	(5.5%)
Perennial allergic coryza and colitis	4 cases	(2.2%)
Perennial allergic coryza and migraine	2 cases	(1.1%)
Perennial allergic coryza, bronchial asthma, and migraine	1 case	(0.5%)
Perennial allergic coryza, pollinosis, bronchial asthma, and migraine	1 case	(0.5%)
Perennial allergic coryza, pollinosis, and eczema	1 case	(0.5%)
Perennial allergic coryza, bronchial asthma, and eczema	1 case	(0.5%)
Perennial allergic coryza and urticaria	1 case	(0.5%)
Perennial allergic coryza, pollinosis, bronchial asthma, and angioneurotic edema	1 case	(0.5%)

TABLE II. PERCENTAGE RATIO OF CAUSATIVE FACTORS IN PERENNIAL ALLERGIC CORYZA

Extrinsic	Intrinsic	Combined Extrinsic—Intrinsic	Total
1 case	36 cases	143 cases	180 cases
0.6%	20%	79.4%	100%

eczema, urticaria, and angioneurotic edema. The incidence of allergic syndrome combinations as noted in our study is presented in Table I.

The most important and distressing complication of perennial allergic coryza is bronchial asthma. This occurred in thirty-six cases (20 per cent). In another twenty cases (11.1 per cent), it was associated as a subdominant allergic manifestation with primary bronchial asthma. In still another group of forty-five cases (25 per cent), it was combined with bronchial asthma in association with other allergic syndromes.

ETIOLOGIC DIAGNOSIS

From an etiologic standpoint, the causes of perennial allergic coryza can be divided into two classes: the nonspecific and specific. The nonspecific causes are particularly sudden changes in temperature, smoke, pungent odors, paint and gas fumes. Though these factors may aggravate or precipitate an exacerbation, they are rendered impotent when the specific causes are controlled. The specific causative factors are inhalants, ingestants, and bacterial haptens. These can be divided into three groups: (1) the extrinsic, (2) the intrinsic, and (3) the combined.

Extrinsic Group.—In the extrinsic group, the specific causative factors are of exogenous origin and consist of inhalants (other than pollen) and ingestants. In analyzing our cases, it was found that the extrinsic group was very small. It has been our experience that practically all the patients with perennial allergic coryza of more than several months' duration, due solely to extrinsic causative factors, very quickly develop a sensitivity to bacterial products. Thus, this group is constantly fluctuating. With the advent of a bacterial sensitivity, these patients merge into the combined extrinsic-intrinsic group. In the entire series, only one case (0.6 per cent) did not develop a secondary bacterial sensitivity (Table II).

Intrinsic Group.—The most important causative factors in the intrinsic group are the endogenous products of bacterial activity. In the complete series, thirty-six patients (20 per cent) (Table II) had a bacterial sensitivity only, hence belong to this group. These patients presented a history of frequent head colds, each of which lasted much longer than the rather short duration (four to ten days) of an acute coryza. The symptoms merged gradually from an acute to a prolonged subacute stage. The latter lasts indefinitely until a fresh insult precipitates the cycle. With each fresh exacerbation, the thin watery discharge becomes a mucopurulent one in which a neutrophilic picture prevails. Slowly, as the character of the discharge again becomes thin and watery, the eosinophiles replace the neutrophiles. The nasal mucous membrane has a dusky red color, and the lower turbinates are boggy and edematous. Sneezing, chronic rhinorrhea, slight itching of the nose, nasal voice, frontal headache, and lassitude were constantly noted. This is the clinical picture of bacterial nasal allergy and is analogous to bronchial asthma of bacterial origin. One might hypothesize a combination of bacterial hapten based upon the Burky phenomenon[4] as a possible explanation for bacterial nasal allergy.

From an etiologic point of view, bacterial allergy of the nose has not received the proper recognition from both allergists and rhinologists. In the past, the bacterial phase of perennial allergic coryza has been categorically classified as chronic infection. In the differential diagnosis insufficient attention has been given to the history, character of the nasal discharge, and the correct interpretation of repeated nasal smears. Perhaps, the classical description of the pale grayish blue color of the nasal mucous membrane has been overemphasized. An allergic nose can and does occasionally present a dusky red mucous membrane. This is not an irreversible reaction, because with proper conservative and specific treatment the normal color can be restored. A comparable duskiness has been noted in the intestinal tract at laparotomy. Marks[3] states that a preoperative diagnosis of acute appendicitis sometimes may become, upon entering the abdomen, a postoperative diagnosis of gastrointestinal allergy characterized by segmental spasm and duskiness occasionally associated with a small amount of bloody exudate. The administration of epinephrine hydrochloride parenterally immediately relieves the spasm and restores the normal color to the affected intestine.

Combined Extrinsic-Intrinsic Group.—This is a very large group, 143 cases (79.4 per cent) being classified in it (Table II). All of these cases at first presented a single or multiple sensitivity, originally due to extrinsic factors. However, with the advent of repeated bouts of nasal infection, a bacterial hapten sensitivity (intrinsic) insidiously developed. Thus, these patients slowly merged into the combined group. This group also includes the patients with pollinosis who complicated their pollen sensitivity with

bacterial nasal allergy. Patients in the combined extrinsic-intrinsic group are really never free of their complaint because the interaction of the causative factors continuously exacerbates their symptoms.

TABLE III. CAUSATIVE FACTORS OF PERENNIAL ALLERGIC CORYZA IN A STUDY OF 180 CASES

1. Kapok (single sensitivity)	1 case	(0.6%)
2. Bacterial hapten sensitivity	36 cases	(20.0%)
3. Single or multiple inhalant and/or ingestant sensitivities in combination with bacterial hapten sensitivity	143 cases	(79.4%)
(a) House dust	94 cases	
(b) Pollens	54 cases	
(c) Foods	37 cases	
(d) Kapok	12 cases	
(e) Dog dander	6 cases	
(f) Cat dander	6 cases	
(g) Feathers	5 cases	
(h) Molds	1 case	
(i) Drugs (aspirin)	1 case	

Skin Tests.—A most essential procedure in establishing the etiologic diagnosis is the correct evaluation of skin tests.[2] The most common causes (Table III), excluding bacterial haptens, were, in the order named, house dust, pollens, foods, kapok, dog and cat dander, feathers, and molds. The major food offenders were cheese, egg, chocolate, shellfish, milk, cereals, spinach, apple, nuts, and banana. The less common food offenders were grapefruit, cucumber, pork, asparagus, tomato, coffee, beets, and mushroom.

Diagnostic Criteria.—The establishment of a clinical and accurate etiologic diagnosis of perennial allergic coryza entails the following pertinent essentials: (1) a thorough history with special emphasis upon the allergic phase, (2) a complete physical examination including routine blood and urine studies, (3) skin tests interpreted and correlated with the allergic history, (4) repeated observations of nasal smears, and (5) x-ray of the paranasal sinuses. Often, despite all these studies and not until the patient demonstrates a continuous clinical improvement, can a physician be absolutely certain that the correct etiologic diagnosis has been established.

TREATMENT

The conservative approach is the keynote to successful treatment. It is based upon the integration of several therapeutic procedures, each one of which when employed singly, indiscriminately, or out of sequence either fails or, at best, produces minimal improvement only. In the treatment of perennial allergic coryza, allergic therapy is the primary medical approach, while rhinologic surgery is secondary and should be reserved for the treatment of allergic complications such as polyps, boggy turbinates, and inadequate drainage. Rhinologic surgery should be employed only after the allergic regimen has been in operation for several months because sometimes, with proper allergic therapy, nasal polyps do disappear, edematous turbinates do return to normal, and adequate drainage can be re-established.

Allergic Hygiene.—Factors which constantly aggravate the patient's complaint must be excluded from the immediate environment. The patient

is instructed to avoid contact with irritating odors from leaky gas or oil stoves, kerosene lamps, gasoline and oil products, electric refrigerators, fresh paint, tobacco smoke, tar, camphor, et cetera. Insect powder is not to be used in the home. The usual dust precautions must be followed. Unless specifically advised, animal pets are not to be kept. Smoking, if not completely eliminated, is to be reduced to a minimum. Protection against exposure to inclement weather and sudden changes in temperature is essential, since the patient must prevent as many bouts of upper respiratory infection as possible. An adequate amount of restful sleep, at least eight hours nightly, is highly desirable. Drugs should be taken only upon prescription. Finally, all foods to which the patient is sensitive are to be eliminated from the diet.

Outline of Treatment.—The following therapeutic measures have been integrated in their proper sequence and, in our hands, have produced highly gratifying results. It cannot be emphasized too strongly that these measures are supplementary to each other and will fail if employed singly. To obtain optimum results, the therapeutic chain must be used in its entirety.

A. Office Procedures.
   1. Nasal decongestants.
   2. Penicillin aerosol intranasally.
   3. Mild silver protein nasal spray.
   4. Desensitization.
   5. Vaccine therapy.

B. Supportive Measures.
   1. Decongestants and mild silver protein nasal sprays.
   2. Antihistamine drugs.
   3. Multiple vitamins oral therapy.

C. Intranasal Surgery.

Office Procedures

Decongestants.—The first step in our treatment is the intranasal administration of a small amount of aqueous ephedrine 1 per cent isotonic solution in heated vapor form. This is followed by a warm spray of Gluco-thricil (an isotonic solution of ephedrine 1 per cent and Tyrothricin 1:5000).

Penicillin Aerosol Intranasally.—A very important agent in the armamentarium of the allergist for the treatment of perennial allergic coryza is nebulized penicillin aerosol intranasally. Crystalline sodium penicillin G, in concentration of 50,000 units per c.c. of distilled water, is combined with 1 c.c. of a 1 per cent isotonic solution of Neo-synephrine hydrochloride. One half c.c. of this solution, containing approximately 12,500 units of penicillin and 3½ minims of 1 per cent Neo-synephrine, is aerosolized at each treatment. In more than 1,000 such treatments, not a single penicillin reaction has been encountered. If the symptoms are severe,

intranasal penicillin aerosol therapy can be administered every other day for three or four treatments; otherwise, once weekly will suffice. An average of six to eight penicillin aerosol treatments will produce highly beneficial results. Oftentimes, only one or two treatments are responsible for a dramatic amelioration.

Mild Silver Protein Nasal Spray.—The intranasal penicillin treatment is followed by a mild silver protein (argyrol type) nasal spray, 10 per cent strength.

Desensitization.—Specific desensitization is not neglected. House dust, pollens, animal dander, and molds receive special attention as indicated. Offending foods can be eliminated from the diet. If this is not practical, oral desensitization can be tried.

Vaccine Therapy.—In our series, bacterial hapten sensitivity was the sole causative factor in thirty-six cases (20 per cent) and a secondary complicating factor in 143 cases (79.4 per cent). Thus, bacterial hapten sensitivity has a phenomenally high incidence. All of these patients were treated with a stock vaccine suspension containing the following organisms, each in concentrations of 200 millions per c.c.: Micrococcus catarrhalis, Bacillus friedlander, Pneumococcus (Types I, II, III), Streptococcus (hemolyticus and viridans), Staphylococcus albus, and Staphylococcus aureus. Injections were given with a syringe graduated in tenths, smaller doses intradermally, larger ones subcutaneously. The first six doses were given at weekly intervals, while subsequent doses, depending upon the clinical progress, were administered either weekly or monthly. The initial dose should be 0.05 c.c., the second 0.1 c.c., the third 0.2 c.c., the fourth 0.3 c.c., the fifth 0.4 c.c., and the sixth 0.5 c.c. At this point, if the symptoms were well controlled, the seventh dose (0.75 c.c.) and the eighth dose (1.0 c.c.) were administered. The latter was repeated at monthly intervals indefinitely. If, however, the patient still had some complaint, the dosage was levelled off at 0.5 c.c. This dose was repeated at weekly intervals until the residual nasal symptoms disappeared, at which time the 0.75 c.c. and 1.0 c.c. doses were given. With this schedule only exceedingly mild constitutional reactions have been encountered, the symptoms consisting of slight headache and malaise which disappeared in a few hours. Vaccine therapy very often produces a spectacular improvement.

Supportive Measures

The patient is instructed to use locally Gluco-thricil solution, a *decongestant, antibiotic nasal spray* followed by a *mild silver protein spray* of the argyrol type (10 per cent strength) twice daily. Decongestants must be employed for a short time only. Kern[1] emphasizes that the too frequent and excessive use of vasoconstrictor drugs is followed by a vasoparalysis and a consequent increase of mucosal edema. Apparently valuable additions to our therapeutic measures have been the introduction of *antihista-*

mine drugs. Employed in recommended doses, they seem to exert a beneficial influence upon the symptoms of perennial allergic coryza and are effective in about 50 per cent of the cases. Potent *multiple vitamins* were administered routinely to all the patients. Within a comparatively short time, they experienced a feeling of well-being, became more alert, and regained their appetite. The administration of these vitamins, because of their tonic effect, was continued indefinitely.

Intranasal Surgery

Edematous turbinates, mucous polyps, and inadequate drainage are often observed in long-standing cases of perennial allergic coryza. If these local complications do not completely disappear or, at least, greatly improve after several months of allergic therapy, then surgical intervention should be considered. When, however, early operation is essential because of the gravity of the complications, subsequent allergic therapy should not be neglected; otherwise, the symptoms persist and the complications, especially nasal polyps, tend to recur. A competent rhinologist should perform the indicated surgical procedures.

RESULTS

The treatment, as described, has produced uniformly excellent results. The nasal symptoms were markedly improved after six to eight weekly treatments. In many patients, a spectacular amelioration was noted after only one to two treatments. Sneezing, itching, nasal discharge, postnasal drip, nasal voice, and frontal headache quickly disappeared. Besides local amelioration the patients also experienced an improvement in their general health. They felt stronger, were more alert and eager, and their appetites improved. In our series of 180 cases, 149 patients (83 per cent) received 100 per cent improvement; twenty-four patients (13 per cent) had 75 per cent; five patients (3 per cent) had 50 per cent. There were two failures (1 per cent), patients in whom no improvement was noted or their symptoms were made worse.

CONCLUSIONS

Perennial allergic coryza is a disease entity. Bacterial haptens, inhalants, and ingestants are the commonest specific causative factors. Its successful treatment depends upon the application of several therapeutic measures, each properly integrated to form a therapeutic chain which embodies the allergic approach as the primary essence of treatment and reserves rhinologic surgery for the treatment of the allergic complications only. Conservative and judicious therapy will produce excellent clinical results.

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A NEW ANTIHISTAMINIC COMPOUND FOR THE TREATMENT OF URTICARIA AND HAY FEVER

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AT least 200 drugs have been offered on the market for the treatment of urticaria and hay fever; but in spite of this large assortment from which to choose, the results have often been inadequate and unsatisfactory. In urticaria, the subcutaneous injection of epinephrine or oral administration of ephedrine might give partial and transient relief from the pruritus. Calcium has been advocated because of its ability to decrease the excitability of the nervous system, but it has produced no detectable relief except when injected intravenously in large doses. When epinephrine, ephedrine, and intravenous calcium have failed, the physician has turned to less hopeful products, as, for example, alkalis, atropine, and the sedatives. The local application of calamine lotion and similar solutions has been of little help. In hay fever, orally administered ephedrine and the topical application of vasoconstrictors have been perhaps the most widely used symptomatic treatments, but they have left much to be desired.

Allergists have, therefore, searched for new drugs which might be useful and have welcomed the appearance of the antihistaminic compounds with some enthusiasm.

The earliest antihistaminic drugs to become available in this country were Benadryl and Pyribenzamine. The excessive drowsiness resulting from Benadryl was a disadvantage. A twenty-eight-year-old woman patient under my care slept for seventy-two hours after taking 50 mg. The incident caused me so much concern that I hesitated to use Benadryl thereafter. Pyribenzamine did not cause the same degree of drowsiness. It was helpful in many cases but failed in many others.

On August 12, 1947, I obtained a supply of Histadyl (Thenylpyramine Hydrochloride, Lilly).* It was thus possible to investigate the usefulness of this drug during the ragweed hay fever season which ordinarily begins in Chicago about August 15. The pharmacology of Histadyl had been reported by Lee, Dinwiddie, and Chen,[1] and a preliminary clinical report was given by Peirce and Mothersill.[2] Chemically the compound is a derivative of ethylenediamine. Its graphic formula is shown on the following page.

DOSAGE AND RESULTS

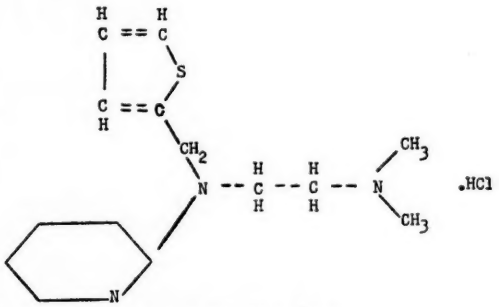
The dosage ordinarily used for hay fever in children was a 25-mg. capsule three to five times daily. For adults, each dose was 50 mg. given in the same manner. In urticaria it was usually necessary to give doses twice as large as in hay fever. A total of twenty-seven patients were treated. The results are given in Table I.

*This compound was originally designated by its laboratory serial number, 01013.

TABLE I.

Type of Allergy	No. of Cases	Results
Hay fever	21	Moderately good to excellent
Urticaria	4	Good to excellent
Serum sickness	1	Excellent
Asthma	1	No value

In hay fever cases, excellent results were obtained only in patients who had received a preseasonal and coseasonal course of injections with allergenic ragweed pollen extracts. Patients who had not had this treatment obtained less satisfactory relief. In order to obtain good to excellent results in urticaria, it was necessary to prescribe 400 to 500 mg. of the drug daily. The drug failed to help the first asthmatic patient treated, and since other antihistaminics had also failed in asthma I preferred to use my limited supply of Histadyl in cases where there was more hope of benefit.



Graphic formula of Histodyl

TOXIC EFFECTS

Three hay-fever patients complained of a dull frontal headache for ten to thirty minutes after taking Histadyl. However, this was not sufficiently serious to justify discontinuation of the drug. Definite drowsiness was not observed, but in most cases there appeared to be a feeling of relaxation. This was desirable in those who were otherwise apprehensive.

Blood counts, urine analyses, and blood pressure readings were obtained in patients who took the drug for six to ten weeks. Systolic blood pressures had a tendency to become lower by 10 to 15 mm. No significant blood or urine variations were noted.

SUMMARY

1. A report of twenty-seven allergic patients treated with Histadyl is given.

2. Except for one asthmatic patient, the results were moderately good to excellent.

3. In ragweed hay fever, excellent results were obtained only in those

(Continued on Page 383)

AN EVALUATION OF THE PATCH TEST BASED ON EXPERIMENTAL FINDINGS

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THE purpose of the patch test is the reproduction of the clinical skin lesion on an uninvolved local area. Since no prior preparation of the skin is entailed, the patch test is also referred to as the surface, contact, or percutaneous test. A positive reaction represents a delayed type of allergic response, the reaction time being approximately twenty-four hours.

The preponderance of evidence fails to substantiate the presence of detectable antibody or the transfer of sensitivity through serum or vesicle fluid. Though the studies of Landsteiner and his co-workers[10] in chemical hypersensitiveness in animals have demonstrated wheal-type antibodies and passive transfer of sensitiveness, these phenomena have not been substantiated in contact dermatitis in humans.

TABLE I. SPONTANEOUS FLARE-UP OF SITES IN SUBJECTS SENSITIZED BY ONE APPLICATION OF EXCITANT—THE INCUBATION PERIOD

Excitant	Number of Subjects	Period of Application	Incubation Period—Interval between Application and Flare-up
Krameria		Days	Days
fluid-extract	5 adults	1	10–21
1.0 g. in 1.0 ml.	2 adults	2	11–12
	1 adult	3	11
	6 adults	7	9–14
	4 children	2	8–15
Limits	18 subjects	1–7	8–21

When a chemical substance, simple or complex in nature, which has shown its ability to act as a potent sensitizing agent is applied experimentally to the human skin, phenomena of both theoretical and clinical importance are observed. One such excitant is krameria,[5] a plant extractive, which has been used by the writer in a series of studies in contact allergy in humans. Thus, application to the skin by patch test of several drops of the fluid extract of krameria for a period of one, two, three, or seven days was followed by the appearance of a contactant-type reaction (papular or vesicular dermatitis) after a lapse of from ten to twenty-one days following the onset of the exposure (Table I). This response was referred to as the flare-up phenomenon.[5,6] The interval between treatment of a site and the appearance there of a reaction was the incubationary period of sensitization of human skin with krameria, and signified the advent of a state of hypersensitiveness in an individual previously non-sensitive. Subsequent testing in the same manner elicited a typical response on removal of the patch test at the end of twenty-four hours or less. This shortened period represented the reaction time in an already sensitive subject. Moreover, it was evident that the entire skin surface was involved, for applica-

TABLE II. SPONTANEOUS FLARE-UP OF SITES IN SUBJECTS SENSITIZED BY THREE APPLICATIONS OF EXCITANT

Case Number	Duration in Days of Applications 1 and 2	Day of Application 2	Reaction After Application	Day of Application 3	Day of Reaction at Site 3	Day of Flare-up at Site 2	Day of Flare-up at Site 1	Inactive Phase of Site 2	Inactive Phase of Site 1
9	2,1 resp.	15	0	22	(24)–29*	(25)–29		(10)–14	
10	1,1 resp.	92	0	99	(100)–106	(102)–106		(10)–14	
11	1,1 resp.	29	0	36	(?)–43**	(?)–42		(?)–14	
12	7,1 resp.	29	0	36	(?)–50	(?)–50		(?)–21	
13	2,1 resp.	15	0	22	(?)–29	(?)–36	(?)–43	(?)–21	(?)–43
14	7,1 resp.	15	0	22	(23)–29	(26)–29	(29)–29	(11)–14	(29)–29

*Number indicates day on which writer observed reaction.
Number in ( ) indicates day on which subject observed reaction.
**(?) signifies that subject did not observe the exact day on which reaction appeared. The reaction obviously occurred from one to seven days prior to its observation by the author.

tion of the test to any part of the body was followed by the appearance of the typical reaction.

Subjects who failed to become sensitized by the initial treatment could become so upon repetition of the patch tests to other areas at intervals of one or several weeks. Thus, nineteen subjects were sensitized by two to five successive applications of the excitant. Moreover, the appearance of a response at the final site of treatment was followed in fifteen subjects by a spontaneous flare-up of the site of the preceding application which up to that time had remained unchanged (Table II). In four additional subjects flare-up occurred at two preceding and previously negative test sites. The interval which elapsed between the time of the treatment of these late responding areas and the appearance of the spontaneous reactions at these sites was from ten to forty-three days, referred to in the tables as the inactive phase. It would appear from these findings that allergenic excitant applied to the surface of the skin had become fixed in the skin cells for as long as forty-three days.

It was observed, furthermore, that flare-up of the sites occurred in the reverse order of treatment, i.e., the final site first, the preceding one next, et cetera, and that the delayed responses were in most instances of lesser intensity than the initial flare-up reactions. To obtain an explanation for this phenomenon, the flare-up reaction was studied further, using graded dilutions of the excitant. The findings indicated that the earliest treated sites had lost most of the excitant, and that their reactivity had diminished during the inactive phase so that it was equivalent to that elicited by a solution many thousand times weaker than the original extract. Thus the spontaneous flare-up of sites in the reverse order of their treatment indicated waning amounts of fixed allergenic substance at the respective areas.

Another study, recently reported,[7] demonstrated that a healed site of contact dermatitis responded to nonspecific stimulation by direct treatment with a second contactant, whereas adjacent uninvolved skin remained non-

reactive. While these findings were primarily related to the subject of so-called local skin sensitivity and the performance of patch tests on healed dermatitis areas, they would suggest, in addition, that antigenic substance remained fixed in the skin at healed specific sites for as long as 128 days.

In summary, then, the cited studies indicate the possibility of sensitizing the entire skin surface by means of the patch-test application of a potent chemical substance in sufficiently high concentration. The allergenic excitant is apparently fixed in the skin and evokes an immunologic response which may or may not be adequate to produce total sensitization. Successive patch test treatments then may evoke such an effect, each single stimulus playing its own cumulative part to bring about the final state of hypersensitiveness.

The clinical implications would seem obvious, namely that diagnostic patch tests with an active excitant in high concentration may induce sensitization even with a twenty-four or forty-eight hour contact. There are a number of reports in the literature giving the incidence of sensitivity to poison ivy as 49 to 76 per cent, whereas analysis of the findings indicate that in many of the subjects sensitivity had been induced by the patch test itself.[3,8,9,14,15,16] A knowledge of the sensitizing potencies of chemicals, as pointed out by Sulzberger[17] and others would minimize such a hazard. Secondly, the not uncommon practice of repeating patch tests with the same allergen, when reactions are negative or doubtful, should be discouraged, since each such exposure can act as an immunological stimulus. It is not improbable, therefore, that the repetition of certain diagnostic patch tests by one or several clinicians may actively sensitize patients to contactants being applied in the tests. The risk from indiscriminate patch testing becomes even more apparent when it is carried out by untrained personnel, including lay cosmeticians.

As another clinical implication, the findings that nonsensitive areas of skin and healed sensitive sites are able to fix allergenic excitant help to explain a number of clinical experiences reported in the literature and undoubtedly encountered occasionally by practicing dermatologists and allergists, namely:

1. The relighting of healed patch-test sites by a repetition of the test with the same substance.[12]
2. The exacerbation of a quiescent or recently healed dermatitis, following patch testing with the specific substance.[4] Actual spreading of the dermatitis may likewise ensue.[1]
3. The relighting of healed patch-test sites following a recurrence of the specific dermatitis.[2]

SUMMARY

Experimental studies in sensitization of the skin of humans indicated that the patch test may be a means of provoking sensitization of the nonsensitive individual. It was also evident that excitant can remain fixed in

the skin for relatively long periods of time. To avoid the hazards incident to the clinical implications of these findings, certain precautions must be observed in the performance of patch tests.

1. The nonsensitizing concentrations of contactants should be known. Detailed lists of excitants may be consulted.[11,13,17,18]

2. Tests with the same or related excitants should not be repeated under certain conditions.

3. Patch tests should not be applied during the active phase of a dermatitis or a recently subsided dermatitis.

4. A patch test with the specific excitant may produce the generalization of a localized active dermatitis.

5. Local testing in previously involved areas may give nonspecific reactions which are not of etiologic significance.

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AN ADAPTER FOR THE RAPID PERFORMANCE OF THE PUNCTURE SKIN TEST

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A SIMPLE adapter for the allergy syringe which facilitates the rapid and uniform performance of the puncture skin test has been devised. The adapter is processed from stainless steel or other suitable metal, and consists of a lateral component about two inches long and two horizontal extensions. The proximal extension consists of a split circular band, which by virtue of its spring action fits snugly around the barrel. The distal component is bored to allow movement of the needle up to its hub. The lateral component rests parallel to the barrel of the syringe, and serves to adjust the adapter upward or downward.

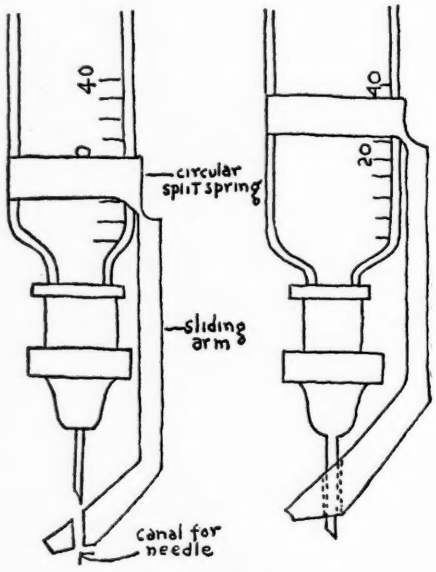

Fig. 1. Adapter for puncture skin testing.

OPERATION

The adapter is slipped over the barrel of the syringe, the hypodermic needle is then attached and the allergen drawn up.

The desired depth of the needle exposed for puncture is obtained by the appropriate adjustment of the adapter.

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TECHNIQUE

The depth of the needle exposed in each case should be determined by the performance of a few preliminary puncture tests. The puncture should not be deep enough to draw blood.

A small drop of the liquid allergen is ejected from the syringe onto the skin of the arm, forearm, or back and the puncture made through it by a rapid plunge of the syringe at such an angle as to facilitate penetration of the skin.

Stoesser[1] recommends three punctures for foods, two for inhalants, and one for pollens. Multiple punctures should be close together.

The preliminary drop of allergen may be dispensed with, especially when testing with pollens, as the author has found that the puncture itself will eject a sufficient quantity of the allergen into the skin to yield a positive reaction in cases where skin sensitizing antibodies to the allergen exist.

SUMMARY

1. An adapter for the allergy (Cooke) syringe is described which facilitates the performance of puncture skin tests.

2. The adapter, once attached to the barrel of the syringe, need not be removed. It does not interfere with the performance of intradermal tests.

3. The puncture technique of skin testing is a rapid, safe (minute quantities of allergen are used) and reliable method of testing and is especially suitable for the testing of children.

520 Crown Street

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MANUAL OF ALLERGY LABORATORY AND DIAGNOSTIC PROCEDURES

The new revised edition of the Manual of Allergy Laboratory and Diagnostic Procedures is ready for the press and will be available by September 1. The old Manual has been completely revised and brought up to date. It will be bound in heavy buckram and will be much larger, giving all details for the making of allergenic extracts and their standardization, various diagnostic procedures and all details essential for the allergist who has his own laboratory for clinical and investigative use. Several hundred orders have been received for this revised edition, and those who have sent in their orders will be notified of details by post card as soon as the new Manual is available.

INDUSTRIAL DERMATITIS CONTROL

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INDUSTRIAL dermatitis is a subject of considerable interest to the allergist because of its compensation implications. Of the many allergic diseases in man this one can usually be supported by allergic proof.*

However, it is important to have a working knowledge of the common skin diseases, as these closely simulate eczematous dermatitis from external causes. Sulzberger enumerates some of the more common non-industrial dermatoses which must be considered in the differential diagnosis. These are seborrheic eczema, psoriasis, lichen planus, dermatitis herpetiformis, erythema multiformi, non-industrial fungus infections, impetigo, drug eruptions, herpetic impetigo, non-industrial dermatitis exfoliativa, atopic eczema, and non-industrial contact type dermatitis such as weed dermatitis.†

As far as industrial dermatitis is concerned, a knowledge of the locations in the factory where industrial sensitizers are located helps in the diagnosis of these. In our experience the greatest incidence of dermatitis occurs in those workers who are exposed to the chemicals used in the color processing of film and paper. At one time the incidence of dermatitis in these workers was as high as 75 per cent. At the present time this has been appreciably reduced so that it is less than 10 per cent. Methods of control have been accomplished by telling the workers the sources of the dermatitis and instructing them in the importance of the immediate neutralization of the chemicals by dipping hands in neutralizers as soon as they know that they have had an undue exposure to the chemicals. Washing of the hands with acid soaps instead of the alkaline soaps, using protective creams to protect the hands, as well as the wearing of rubber gloves when possible, is suggested.

Despite the above precautions some employes acquire dermatitis which usually subsides under treatment. The decision must then be made whether it is advisable to return these men to their former exposure or to another job. However, because of the phenomenon of hardening, which means the ability of the skin to build up a tolerance to chemicals formerly not tolerated, these patients can and do resume their former work. Such a practice is supported by evidence presented by Peck et al,** and is confirmed by our experience.

A word of caution should be added at this point. Care must be taken that the concentration of the chemicals which caused the dermatitis is not exceeded, as this will precipitate another episode of dermatitis.

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*Sulzberger: Dermatologic Allergy, page 87.
†Sulzberger: Dermatologic Allergy, page 467.
**S. M. Peck, et al: Industrial Med., 14:214, (March) 1945.

The hardening process is not permanent. Workers who are away from their jobs for a period of time, such as during illness or vacations, may again develop the dermatitis when re-exposed to their former job.

It is interesting to note that some patients never acquire a tolerance. These workers, of course, must be transferred to a job in which there is no chemical contact.

The control of dermatitis in industry is the combined responsibility of both the engineering and medical departments. It is, of course, the obligation of the latter to screen, first of all, new chemicals for their primary irritant and antigenic properties by patch testing guinea pigs. The next step is to observe the effects of these chemicals on the workers who are exposed to them. Obviously, chemicals of lower antigenic potential are substituted for those of higher potential wherever possible.

A most important factor in the control of dermatitis in industry is the selection of the man for the job. Workers with skin diseases, or with a history of allergy usually are ineligible for jobs which involve chemical exposure. This is because they are regarded as bad risks. Sulzberger summarizes the reasons as follows: "The existence of a non-industrial dermatosis may predispose to industrial dermatitis; and on the other hand industrial exposure may elicit attacks, prolong the course, or produce exacerbations of a non-industrial dermatosis."††

Education of employes must be undertaken concerning chemical sensitization so that they may avoid undue and prolonged exposure whenever possible. The hands may be protected with the use of protective creams, acid soaps, wearing of rubber gloves where needed, or by dipping hands in neutralizers after exposure to chemical sensitizers.

The most important step in the general treatment of industrial dermatoses is the removal of the patient from the chemical exposure which has precipitated the dermatitis. Attention is next directed to the control of itching because scratching may aggravate the dermatitis and increase the pruritus. The new antihistaminic drugs, Benadryl and Pyribenzamine, are the drugs of choice for the control of itching.

Following this, local treatment is instituted in the form of wet dressings, using solutions of potassium permanganate, aluminum acetate, or boric acid depending on the severity of the dermatitis. These, together with soothing lotions, such as tragacanth or calamine, and indicated ointments, comprise the treatment routine.

In addition the patient is cautioned to avoid skin irritants in his daily routine while at work or at home. The irritants to be avoided are soap and water bathing, paints, gasoline, shaving material, shampoo, nail polish, garden sprays, dusts, et cetera. One of the acid soaps is suggested as a substitute for the ordinary soaps.

Whenever a sensitized worker develops a dermatitis after a second exposure to a chemical with which he is working, the reaction in the skin

††Sulzberger: Dermatological Allergy, page 467.

does not stop at the moment that the antigenic contact is broken. In general, the patient's skin condition becomes worse before it subsides, regardless of the general or local measures carried out. It is important to inform these patients of this fact, not only that they may be reassured but also that they may not be disposed to lose confidence in the treatment and consequently seek other medical advice.

SUMMARY

The incidence of industrial dermatitis can be controlled by:

1. Skillful selection of men for jobs which involve chemical exposure. Eliminating those who have active or potential skin diseases.
2. Screening of new chemicals for irritant and antigenic properties by patch testing guinea pigs before exposing workers to them.
3. Substituting chemicals of lesser antigenic properties for those of greater antigenic potentialities whenever feasible.
4. Education of employes who are exposed to chemicals concerning chemical sensitization, so that they may avoid undue or prolonged exposure whenever possible, with emphasis on the use of protective creams, rubber gloves, and hand hygiene.
5. Seeking medical attention when the skin tolerance is exceeded.

NEOHETRAMINE IN THE TREATMENT OF EXPERIMENTAL TUBERCULOSIS

(Continued from Page 319)

is indicated not only in human tuberculosis, but also in other infectious diseases, such as leprosy, which display important allergic components. Although experiments are in progress in our laboratories to confirm and extend our findings, it is hoped that this preliminary report will stimulate additional investigations in other laboratories.

SUMMARY

Neohetramine exerted a beneficial effect on the course of experimental tuberculosis in guinea pigs, although in the regimen employed it failed to influence the reaction to 1 mg. of Old Tuberculin administered intracutaneously.

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THE CLINICAL SIGNIFICANCE OF ACETYLCHOLINE

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EVIDENCE has gradually accumulated that acetylcholine is a factor in certain reactions which appear allergic. In discussing this evidence it is necessary to recall the normal functions of acetylcholine in the skin No attempt will be made to discuss the activities of this compound at motor nerve endings, at the synapses of peripheral ganglia or at synapses in the central nervous system, which are doubtless of vast clinical significance.

Most effects of stimulating the parasympathetic nervous system are caused by the release of acetylcholine at nerve terminals.[4,5] One of its characteristic effects is vasodilatation. Its local release at nerve terminals is probably the cause of vasodilatation in the skin, although the anatomical course of the responsible vasodilator fibers is in doubt. The sweat glands are innervated by fibers which, although anatomically running through the sympathetic system, liberate acetylcholine when stimulated. The flare about a histamine wheal is produced by an axon reflex running through sensory nerves and Wybaugh[23] has demonstrated release of acetylcholine at these sensory nerve terminals.

All the above activities of acetylcholine are potentiated by prostigmine and blocked by atropine and are among the muscarine-like effects of the drug. Recently Rothman and Coon[19] have shown that acetylcholine causes two interesting effects in the skin which can be produced also by nicotine. First, the intradermal injection of acetylcholine stimulates a contraction of the surrounding erector pilae muscles, producing the appearance of local goose flesh. This stimulus is carried through an axon arc localized in the skin and is effected by the liberation of sympathine at the terminals about the erector pilae muscles. The same investigators demonstrated in the zone surrounding an intradermal injection of acetylcholine that there was a stimulation of sweat glands again effectuated through an axon reflex arc, at the end of which acetylcholine is liberated. Perhaps of more significance, although less conclusive, is the evidence brought by Rothman and Coon[20] that acetylcholine is liberated in the wheal produced by histamine and is present in some inflammatory lesions of the skin.

These properties of acetylcholine are of interest because they throw light on the mechanism of some of the clinical phenomena called physical allergy.

Duke[7,8] introduced the term "physical allergy" to denote reactions resulting from heat, cold, light and mechanical stimuli. He reported instances of asthma, vasomotor rhinitis and conjunctivitis, photophobia, erythema, pruritus, eczema, abdominal pains and shock, but the majority of his cases were of urticaria with or without angioneurotic edema. He includes in this group factitious urticaria, the urticaria which occurs in certain indi-

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viduals on exposure to light, the urticarias produced by exposure to cold and those produced by exposure to heat. Among the heat-reacting cases Duke recognized two groups: one in which local application of heat produced wheals limited to the exposed areas, and another group in which anything which raised the body temperature, such as local or general exposure to heat or violent exercise, produced an outbreak of hives. In this second group similar outbreaks were caused by purely psychic stimuli.

Duke's descriptions of his cases were circumstantial and most of us could recognize among them examples parallelling cases in our own experience. The clinical phenomena were indistinguishable from those known to be caused by the chemical reaction of antigens and antibodies, but there seemed no tenable hypothesis as to how these physical agents could produce the same effect.

Since Duke's work, a number of observations have been made which point to mechanisms by which these purely physical stimuli may produce chemical effects without invoking any concept of the conversion of energy into matter. The similarity of the urticarial reactions to the histamine wheal made it probable that the wheals of physical allergy were like other wheals produced by the release of a histamine-like substance. Strong evidence in support of this was brought by Horton and Brown[15] who studied the gastric secretion of hydrochloric acid during outbreaks of urticaria from cold. There was a typical rise in secretion of hydrochloric acid during such attacks. The shock that occurs during severe outbreaks of cold urticaria also seems best explained by the release of a histamine-like substance. To this extent, then, the effects of physical stimuli seem mediated by a chemical agent. The hypothesis that light may cause lesions by acting on a photodynamic substance is generally accepted as explaining reactions which have followed injection of hematoporphyrin or those occurring in patients excreting uroporphyrin. Stein[21] reported that intradermal injection of serum from a case of hydroa estivale sensitized normal skin to light, and similar findings have been made in other forms of hypersensitivity to light.[3,17] Blum[2] and his associates have postulated the presence of a photodynamic substance to explain cases of urticaria solare in which passive transfer failed. None of these hypotheses invoke an allergic mechanism.

On the other hand, Gay Prieto,[19] Rajka[18] and, more recently, Sulzberger,[22] Baer and Blum[1] have succeeded in passive transfer of urticaria solare. The reaction in the passively sensitized skin was in these cases urticarial, which suggested an allergic mechanism. The hypothesis was advanced that light altered some tissue constituent, probably a protein, so as to give it antigenic properties. At least it has been shown in a number of instances that hypersensitivity to light is due to substances present in the blood serum.

Harris, Lewis and Vaughan[13] in studying cold urticaria found that it was of relatively frequent occurrence in congenital syphilitics with parox-

ysmal hemoglobinuria. By passive transfer of the serum from these patients they brought evidence of a dermatolytic antibody which combined with the cells of the skin at low temperature, just as the Donath-Landsteiner antibody united with red cells in the cold. By absorption of the sera with red cells of sheep they were able to remove the hemolytic but not the dermatolytic antibody, indicating that the two were distinct. This revealed one method by which physical stimuli could induce an antigen-antibody reaction with its ensuing allergic symptoms.

In 1936 Grant, Pearson and Comeau[11] published their studies on Duke's second type of heat urticaria. The spontaneous attacks in these patients occur after just those stimuli which release acetylcholine in the skin. Generalized attacks could be induced in these patients by subcutaneous injection of a stable analogue of acetylcholine. On skin test, reactions were produced by choline compounds analogous to the wheals produced in routine tests for allergy. These findings suggested another mechanism by which physical stimuli may produce allergic effects.

The hypotheses suggested to explain the mechanism by which physical stimuli act may be summarized as follows:

1. Light sensitivity might be explained by the presence of a photodynamic substance without assuming an immunological mechanism.
2. Proteins or other normal skin constituents might be altered by physical agents and act as allergens.
3. Acetylcholine released by physical stimuli might act as an allergen.
4. One physical agent (cold) may effectuate the reaction of an allergen and antibody already present.

In support of this last hypothesis we have a well-established analogy in paroxysmal hemoglobinuria and the passive transfer experiments of Lewis. The first three suggestions are hypothetical, but for the third there is much supporting evidence which warrants consideration.

Patients with generalized heat urticaria are familiar. They develop hives after hot baths, after violent exercise and also if they are excited or nervously upset. After a severe outbreak they fail to respond to any of these stimuli for a period which may be as long as twenty-four hours. The clinical appearance in these cases is almost diagnostic. The wheals are quite unlike those occurring in other types of urticaria. They are small and bead-like, rarely over 5 mm. in diameter, and are surrounded by brilliant flares 4 to 8 cm. in diameter. Cases are not infrequent which react to the same stimuli with these brilliant large flares and a variable degree of pruritus without producing any visible wheal. Nomland[16] has described patients subject to acute attacks of severe pruritus without wheals, in whom the attacks could be reproduced by Mecholyl.

Not all cases of psychogenic urticaria belong to this group. Patients who are not demonstrably sensitive to heat, some of whose attacks are due to known allergens such as food, occasionally have severe outbreaks from

psychic stimuli. It has been frequently claimed and seems fairly well established that hives can be induced in some individuals by suggestion. In such cases the wheals do not have the morphological character seen in typical cases of heat urticaria, and the mechanism of their production may well be different. The following observations probably do not apply to this group or to the group of persons described by Duke who develop local urticaria in areas exposed to heat.

The studies of Grant, Pearson and Comeau did much to elucidate the mechanism of generalized urticaria caused by heat. Experimentally, attacks may be induced by a number of procedures. If the entire body is placed in a hot cabinet, hives begin to appear as soon as the rectal temperature is increased from 0.4° to 1.2° F. They can be produced simply by wrapping the patient in a hot blanket or by making him exercise when heavily dressed. The most regular and marked response is obtained by heating one area—for example, placing one lower leg in a tub of hot water. When this is done, hives appear on all parts of the body except the immersed limb, which becomes profusely flushed. The absence of whealing in the exposed area is probably because the increased superficial circulation in the limb rapidly carries away any H substance produced there.

If a cuff is placed above the heated area tight enough to occlude the venous return, the urticarial effect is not observed. If the cuff is released while the leg is still being warmed, urticaria appears after a short delay, but if the patient's leg is cooled before the cuff is released, no reaction occurs. This indicates that it is the warming of the blood transported from the immersed limb and not the addition to it of a chemical agent that produces the reaction. In one of Grant's experiments the forearm was congested by a cuff on the upper arm and the cuff then tightened sufficiently to occlude the arteries before the legs were placed in hot water. Bluish areas of vasodilatation were observed developing on the congested forearm, indicating a nerve and not a circulatory stimulus to this area. When the cuff was released and circulation restored, hives rapidly appeared at the spots of previous vasodilatation and elsewhere on the arm. In fact they were more numerous in the area distal to the cuff than on the other limbs or trunk and confluent in a band where the cuff had pressed. The intensified effect was probably due to something retained in the skin while the circulation was occluded. These experiments indicate the following course of events: Warm blood from the heated part is carried to some nerve center. From this center stimuli are sent out through the nerves to the areas in which hives develop.

That the development of hives was due to the release of acetylcholine was shown by Grant in two ways. If a solution of acetylcholine was placed under a negative electrode and a galvanic current passed through the body, a bright flare developed in the area under and around the electrode, and in the covered area a group of small round wheals frequently appeared. The effect could be more regularly produced if prostigmine were

added to the acetylcholine and carried into the skin at the same time, or if a more stable analogue such as acetyl-beta-methylcholine (Mecholyl) or carbominoylcholine chloride (Doryl) were used in iontophoresis. The reaction could be prevented by previous iontophoresis with atropine. They also showed that the subcutaneous injection of Doryl produced a general outbreak of typical hives in these patients, but not in normal individuals. Outbreaks could also be produced, as had previously been shown by Marchioninni and Ottenstein, by injections of pilocarpine. None of these effects could be produced in normal individuals or in those subject to urticaria from other causes.

Tests by intradermal injection give less convincing results but are of considerable interest.[14] Acetylcholine itself causes no distinctive reaction in these patients because of its quick destruction. Mecholyl or Doryl never produce spreading wheals with pseudopods like those produced by the common protein allergens. In a sensitive individual they cause a dome-shaped wheal perhaps larger than those produced in non-sensitized controls but not convincingly so. The most regular reaction in the hypersensitive patient is a wide flare. Frequently, in this flare a group of pinhead satellite wheals appear surrounding the large wheal produced by the injection. Their appearance suggests that the release of acetylcholine at the ends of the same reflex arcs which produce flares in normal individuals after injection of histamine, produces wheals in these individuals who are hypersensitive to acetylcholine.

Attempts to demonstrate an antibody in the serum of these patients by passive transfer have failed, and no attempts have been reported to induce allergy to acetylcholine. However, the hypothesis which would seem to explain these phenomena is that in the individuals concerned acetylcholine acts as an antigen or hapten, and that under any of the conditions which cause release of acetylcholine in the skin these hypersensitive individuals react by the secondary release of a histamine-like substance and the production of wheals.

The findings in this cholinogenic urticaria are of special interest because the reactions are produced not only by physical but by psychic stimuli.

Ever since Hippocrates, physicians have been impressed by evidence of the influence of mind on disease. The observed sequence of events often indicates that not only a subjective feeling of illness or a physiological reaction but actual chemical and structural changes in tissues have been caused by purely psychic stimuli. The apparent effects of such stimuli frequently mimic diseases which we consider allergic. A familiar example is allergic eczema. Patients who in infancy suffer from an eczema demonstrably due to their development of antibodies for specific foods often develop in adolescence a more chronic type of eczema. In some cases this is also an expression of food allergy. In other cases identical lesions seem to be caused by purely psychic disturbances.

The therapeutic successes of cults which treat disease only psychologi-

cally and the demonstrated effectiveness of psychotherapy are additional evidence of the psychic etiology of physical disease. This evidence has long been difficult to accept because no method has been demonstrated by which psychic stimuli could produce anatomical lesions. We seem to have a clue to the problem in the reactions of these patients with heat urticaria to acetylcholine.

The significance of acetylcholine may not be limited to this infrequent syndrome. It is interesting that Rothman and Coon[19] obtained reactions suggesting the presence of acetylcholine in fluid from lesions of allergic eczema and dermatitis herpetiformis—two diseases in which psychogenic factors are believed effective. Duke[9] noted functional cardiac disturbances in his heat-sensitive patients. Hall, Ettinger and Banting[12] were able to produce hyalin degeneration of the coronaries and myocardial degeneration or infarction in dogs by long repeated injections of this drug. In some young dogs similar doses caused hematemesis and melena. This again is evidence of the production of lesions by a chemical agent which is frequently released by psychic stimuli.

The character of the psychic stimuli which release acetylcholine has never been defined, but it may be possible to distinguish between adrenergic and cholinergic emotions. Two of Grant's patients developed lesions when stripped before a class for demonstration, others when they came to the laboratory for tests. One of our patients on whom we had made many gastric tests broke out at the sight of a stomach tube. One of Duke's cases had attacks when negotiating difficult business deals. Pleasant emotions have also been reported effective, e.g., watching an athletic contest (Duke) or anticipation of a dance (Grant). However, the effective emotions could usually be described as embarrassment, annoyance or apprehension. Cannon observed that pain, hunger, fear and rage in animals caused a discharge of adrenaline. He noted, however, that fear also stimulated the sacral parasympathetic. A reaction of defense was probably involved in the fear which he studied, whereas the milder apprehensions noted in our patients involved little such reaction. Diethelm and his associates[6] studied the effect on rabbit gut of blood withdrawn from patients under various emotional stresses. They concluded that anxiety, resentment and anger "are accompanied with definite adrenergic factors" and "tension and possibly fear with cholinergic effects."

The observations here reviewed are important as evidence of the clinical effects of physical and psychic stimuli. Any deductions drawn from them are uncertain. They indicate, however, lines of study that may clarify the mechanism of important psychosomatic reactions.

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A NEW ANTIHISTAMINIC COMPOUND FOR THE TREATMENT OF URTICARIA AND HAY FEVER

(Continued from Page 367)

patients who had received preseasonal and coseasonal injections of allergenic extracts.

4. Untoward side reactions were negligible.

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THE TREATMENT OF BRONCHIAL ASTHMA WITH ISUPREL

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IT is the purpose of this report to review the literature on a new synthetic sympathomimetic amine, -1-3'4' dehydroxy phenol -2- isopropylaminoethanol $(HO)_2C_6H_3CHOHCH_2NHCH(CH)_3$, named Isuprel, which is hailed by its investigators as a new and effective therapeutic drug in relieving the dyspnea of an asthmatic attack. It is also the purpose of this paper to discuss my experiences with this drug in a small series of cases.

It is claimed that Isuprel is a potent sympathetic amine which can elicit responses in the body similar to those of adrenaline, and that it has a pronounced broncho-dilator activity, a marked peripheral vasodilating action, and a good smooth-muscle relaxing ability.

From 1940 to 1946 several European investigators discussed the use of a drug known as Aleudrin which had the exact chemical formula as Isuprel. This Aleudrin was reported to be an effective anti-asthmatic when used as a simple spray. It was further claimed that the crises of experimental dyspnea induced in healthy subjects by the uses of choline aerosols could be controlled. R. Rosser and Dautrebande, Philippot, Charlier and Dumoulin also showed by their experimental work that Aleudrin could relieve the bronchial spasm induced by pilocarpine, ten times more rapidly than ephedrine.

In the U. S. the experimental work of M. S. Segal and J. F. Beakey with Isuprel[6,7] marks the first and only reports, as far as is known, on the drug. In this first report they analyzed the results of studies in eighty-two ambulatory patients with chronic bronchial asthma, and concluded that Isuprel was effective in relieving the dyspnea of bronchial asthma by three routes of administration, namely, oxygen aerosolization with doses of 1.0 c.c. of 1:100 dilution every three hours; subcutaneously with doses of .20 to .33 c.c. of 1:1000, and orally with doses of 30 to 90 mg. daily. They also showed that there was subjective relief from bronchospasm, together with improvement in the vital capacities and freedom of expectoration, as well as minimal undesirable pressor effects and tachycardia.

However, they cautioned as to reactions if more than 0.5 c.c. of 1:1000 was given subcutaneously and they suggested smaller doses on sensitive patients.

In their second and more comprehensive report on this drug, Segal and Beakey reiterated the results of their initial findings and included these additional findings:

1. The fluctuations in blood pressure in asthmatics, that is, the variation in the systolic and diastolic readings in inspiration and expiration were effectively abolished or markedly decreased, especially when the bronchospasm was greatest.

Doctor Lipman is an Associate Fellow of The American College of Allergists.

2. The epinephrine-fast state observed in eleven patients responded favorably with no fastness to Isuprel being observed.

It is the purpose of this report to discuss the office and home treatment of twenty-three ambulatory asthmatic patients with Isuprel. This paper is also concerned with a new route of administration—the sublingual, as well as the oral and subcutaneous routes. (As far as is known, no reports of results of treatment via the sublingual route have been made previously.)

My experience with Isuprel began in November of 1947. It was used in a series of twenty-three cases of bronchial asthma under treatment at my office and at patients' homes. The patients ranged from three and one-half to eighty-four years of age. Eight were males and fifteen females. These patients were currently under treatment for bronchial asthma, and some had been receiving either desensitization injections or various antihistaminics, ephedrine, the barbiturates, aminophylline or epinephrine at various times for the dyspnea of asthma. The desensitization injections on these patients were continued, but all drug treatment other than Isuprel was discontinued.

Each patient except the girl of three and one-half years was given a supply of Isuprel (5.0 mg. sublingual and 10 mg. Isuprel oral) with the instructions to dissolve the sublingual preparation under the tongue for each acute attack of wheezing and dyspnea. This was to be repeated once within thirty minutes if some relief was not obtained, and repeated again within fifteen to thirty minutes if any dyspnea persisted. Thereafter, one to two tablets (10 to 20 mg.) of the drug were to be taken orally every four hours. If insufficient relief was obtained, the patient was instructed to call me. The patient was then given .1 to .3 c.c. of Isuprel subcutaneously. The three and one-half-year-old girl was seen at home during two episodes of acute and very severe dyspnea of bronchial asthma which followed a severe cold. She was given .05 c.c. of Isuprel subcutaneously, with relief within five minutes on each occasion. Such relief lasted eight hours after the first injection of Isuprel, and after the second injection no further dyspnea was observed. The child was free of asthma for a period of about three months when last heard from.

The remaining results of treatment with Isuprel, together with the side reactions or complications, are tabulated in Tables I and II.

It will be observed that no attempt was made to determine the vital capacity changes or blood pressure fluctuations because of the inability to see all these patients immediately during their attacks and following the attacks. However, it was possible to observe the degree of relief obtained, as well as to determine the side reactions from the data presented by the patients themselves. In addition to the supply of the drug, the patient received a card of instructions requesting the following data: first, the severity of the asthmatic attack; second, the amount of relief obtained following the first, second and third doses—if such extra medication was

TABLE I. THE TREATMENT OF BRONCHIAL ASTHMA WITH ISUPREL

Patient	Age	Sex	No. of Yrs. Asthma	Type of Previous Treatment for Asthma	Results of Previous Treatment	Side Reactions From Previous Treatment	Treatment with Isuprel Sublingual	Oral	Subcutaneous	Reactions
A.P.	24	F	2–3	Ephedrine and Amytal cap.	No relief	None	5 mg. tab. Relief in 15 min. Recurrence of dyspnea in 2 hrs. 5 mg. Relief in 25 min. Recurrence in 4 hrs.			Palpitation Nervousness
				Adrenaline 0.5 to 1 c.c.	Relief in 20 min. with recurrence within 1–3 hrs.	Palpitation Nervousness Faintness Nausea		10 mg. Every 4 hrs. Stopped — not enough relief	Refused	Palpitation Weakness Nausea
D.M.	14	F	2	Tedral 3 gr. Aminophylline 3½ Adrenaline 0.5 c.c.	Relief 1–2 hrs. Relief 4–6 hrs. Relief in 10 min.	None None Palpitation Weakness Nausea	5 mg. Relief in 10 min. for 1 hr. 5 mg. Relief in 10–20 min. for 1 hr. 5 mg. Relief in 30 min., lasted 30 min.			Severe palpitation and faintness
								10 gr. every 4 hrs. Relief in 5 min. No recurrence for 48 hrs. Stopped		Palpitation
E.B.	36	M	28	Ephedrine Calc. gluconate Amesic Tedral Adrenaline 1:1000 (1 c.c.)	None None Slight Slight Fair but became adrenaline fast	None Palpitation Faintness Nausea	5 mg. Relief in 10 min., lasting 1–2 hrs. Taking above 2–4x a day	No relief in ½ hr.		None
A.Y.	64	F	15	Aminophylline intramuscularly Tedral Amesic	Relief for 4–5 hrs. Slight Relief in 45 min. for 2–3 hrs.	Dizziness Nausea and vomiting Precordial pain None Slight palpitation	5 mg. Relief in 20 min. 5 mg. Slight relief in 30 min. 5 mg. 45 min. later. Relief for 24 hrs.	60 mg. in 30 hr. No marked relief. Patient stopped treatment of above	Refused	
J.W.	84	M	22	Ephedrine ¾ gr. Adrenaline 1 c.c.	Slight relief with recurrence in 1 hr. Relief	None Severe palpitation. Nausea, Faintness Dizziness	5 mg. Relief in 8 min., lasted 1 hr. 5 mg. Relief in 15 min., lasted 4 hrs. 2–5 mg. tab. at 2 hr. intervals. Relief in 10–20 min.	10 mg. T.I.D., thereafter comfortable	None used	None

M.C.	55	F	11	Ephedrine and Amytal Adrenaline .5-1 c.c.	Slight relief for 30–60 min. and recurrence Relief—recurrence in 4–6 hrs.	None Severe weakness Nausea Vomiting Headaches	5 mg. Relief in 15 min. for 5 hrs. (2nd tab.) 5 mg. Relief in 15-20 min. less relief	60 gr. in 24 hrs. Slight relief only	2 c.c. Relief in 10 min. No recurrence	None
M.L.	68	F	27	Ephedrine Adrenaline 1 c.c.	No relief Taken frequently every day, 5–6x during acute attacks and relief few min. to 1 hr. States it is less effective than previously	Palpitation Faintness Nausea	5 mg. No relief in 20 min. 2nd tab. of 5 mg. Moderate relief. Severe palpitation and nausea		.15 c.c. Relief in 10 min. for 3–4 hrs.	Palpitation Faintness Dizziness
F.D.	76	M	30	Aminophylline 3½ gr. Adrenaline 1 c.c.	Relief for 2–3 hrs. No relief after first few yrs. of use.	None Palpitation Weakness Nausea Vomiting	1st tab. 5 mg. No relief in 20 min. 2nd tab. 5 mg. No relief	80 mg. in 24 hrs. Slight relief only	.2 c.c. Mod. relief. 32 c.c. Complete relief in 10 min.	Slight palpitation
E.N.	15	F	3	Tedral Adrenaline .5 to 1 c.c. Aminophylline intramuscularly 3½ gr.	Slight Good Fair	None Severe palpitation Weakness Vomiting Nausea Nausea and vomiting	1st 5 mg. tab. Mod. relief in 12 min. 2nd 5 mg. tab. No complete relief in 30 min. 3rd 5 mg. tab. Still some dyspnea		.1 c.c. Complete relief of dyspnea for 4 hrs. .15 c.c. Relief for 12 hrs.	Palpitation Faintness Palpitation for 15 min.
R.N.C.	64	F	15	Ephedrine ⅜ to ¾ gr. Adrenaline .5 to 1 c.c.	No relief Relief	Palpitation Palpitation Nausea Vomiting Diarrhea	1st 5 mg. tab. Partial relief in 10 min. 2nd 5 mg. in 30 min. More relief but some dyspnea	60 gr. in 24 hrs. Slight to mod. relief	.2 c.c. Relief prompt Relief in 10 min.	Mod. palpitation and nausea for 30 min. Severe palpitation and nausea for 10 min.
M.C.	32	F	4	Ephedrine Tedral Adrenaline .5 to 1 c.c.	Sl. relief Mod. relief Complete relief	None Palpitation Faintness Nausea	1st 5 mg. tab. Good relief in 10 min. for 2 hrs. 2nd tab. of 5 mg. Relief in 10–15 min.	60 gr. in 36 hrs. No further attacks.		Some palpitation after each dose

TABLE I. (Concluded)

M.E.	56	F	8	Tedral Aminophylline gr. 3½ Adrenaline .5 to 1 c.c.	None Fair Good	None Nausea and flushing Palpitation Weakness Nausea and vomiting	1st 5 mg. Relief in 15 min. 2nd 5 mg. Improved but not completely relieved	Refused		Severe palpitation and weakness. Refused further medication
J.B.	42	M	2	Ephedrine ⅜ to ¾ gr.	Fair	None	1st 5 mg. Slight relief in 10 to 15 min. 2nd 5 mg. Mod. relief 10–15 min. 3rd 5 mg. No further relief	80 mg. in next 36 hrs. Still slight dyspnea	Refused	None
H.G.H.	48	F	4	Ephedrine ⅜ to ¾ gr. Tedral	None to Slight. Slight	None None	1st 5 mg. stat. Relief in 5 min. 2nd tab. Relief in 5–10 min.			Severe palpitation Palpitation
M.H.	58	F	13	Ephedrine ¾ gr. Tedral Adrenaline	Fair Fair Good for few hrs. only	None Palpitation and faintness	.5 mg. Relief in 10–15 min., lasted 30–40 min. .5 mg. Relief in 10 min. 30–40 min. relief only	10 mg. 4x daily. Slight to fair relief	.15 c.c.	None None Slight
W.L.	11	M	3	Tedral Amodrine Adrenaline .25 to .5 c.c.	Fair Fair Good for 1–3 hrs.	Palpitation and nausea	5 mg. Partial relief, in 8–10 min. for 1 hr. 2nd 5 mg. Relief for 30–60 min.	10 mg. 4x daily. Good relief		Slight palpitation and headache
M.K.	26	M	5	Ephedrine gr. ⅜ Tedral	Fair Fair	None None	.5 mg. Relief in 10–15 min. for 2–3 hrs.	None		Mod. palpitation ½ hr. after tab.
G.H.	38	F	8	Ephedrine Aminophylline intravenous 3¾ gr.	Fair Good	Slight palpitation Flushing Weakness	.5 mg. Good relief in 10 min. for 20 to 40 min. 2nd Relief for 1 hr.	10 mg. 4x daily. Fair relief		Some palpitation after sublingual and oral tab. for 15–40 min.
H.S.	54	F	16	Tedral Amesic Adrenaline .5 to 1 c.c. every 1–2 hours	Poor Good but becoming less effective	None Palpitation and some nausea	.5 mg. No relief in ½ hr. 10 mg. Slight relief in ½ hr.	None	.2 c.c. moderate .4 c.c. complete for 3 hrs.	None
H.S.	73	F	30	Asthmador powder Pyribenzamine	Slight to mod. relief None	None	.5 mg. Relief in 15 min. No further attacks	30 mg. daily		None
M.W.	61	F	20	Cough mixtures?	Slight relief	None	5 mg. Relief in 10–15 min. for sev. hrs.	Not given	Not given	Palpitation Palpitation for ½ hr. after taking.
H.N.	36	M	5	Ephedrine Adrenaline	Slight to mod. relief Complete	Palpitation Palpitation and nausea	5 mg. Slight relief in 10–12 min. 5 mg. Moderate relief. 5 mg. No further relief	60 mg. in 24 hrs. No complete relief	.3	Relief. Palpitation for 10–15 min.

required; third, the follow-up relief with the oral tablets; and fourth, the list of side reactions or complications which they might have experienced.

TABLE II. SIDE REACTIONS FROM ISUPREL

	Sublingual	Oral	Subcutaneous
Palpitation	6	4	6
Weakness	1	2	3
Nausea	3	1	2
Vomiting	0	0	0
Headache	1	0	0
or			
Throbbing	1	0	0
Nervousness	2	1	0
Sweating	0	0	0
Dizziness	0	0	1

SUMMARY

It will be noted that of the twenty-three patients treated, eight were males and fifteen females. Of these, twelve had a chronic type of asthma and ten, the paroxysmal type. The attacks of dyspnea varied from mild to severe, nine patients describing the attacks as mild to moderate and thirteen patients classifying them as severe. Out of the twenty-three cases treated, all used the sublingual tablets of Isuprel, nine the sublingual and oral tablets, and eight required sublingual, oral and subcutaneous treatments. Twelve patients out of the total were completely relieved of one or more attacks within five to thirty minutes by one 5 mg. tablet of Isuprel sublingually. In eleven, the relief persisted from one-half hour to several days at a time. Eight patients received only partial or slight relief from the first .5 mg. tablet sublingually and required one or more doses of the subcutaneous injections for complete relief. Two of the patients were not at all relieved by the sublingual and oral routes of treatment. Seven patients were kept comfortable and free from severe dyspnea by the use of oral tablets (after the initial relief with the sublingual Isuprel). Eight patients were relieved by the subcutaneous injections of Isuprel.

Out of the twenty-three patients, fourteen had side reactions ranging from mild palpitation to severe palpitation, weakness and nausea (Table II).

Of the seven patients receiving the subcutaneous injections of Isuprel, there were two who had been adrenaline-fast. The other five had had various side reactions after the use of adrenaline. Out of the twenty-three patients, five refused further treatment with Isuprel after three doses of the sublingual tablets, because of the side reactions, and four patients refused to continue the oral treatment for the same reason.

CONCLUSIONS

1. Isuprel sublingually is a good adjunct in the treatment of the dyspnea of bronchial asthma, although side reactions are common with its use.

2. Isuprel subcutaneously proved the most valuable drug of this group because its action was comparable to that of epinephrine and because it

(Continued on Page 440)

Reports in Brief

Papers appearing in this section were read By Title at the Fourth Annual Session, The American College of Allergists, held in New York City, March 12, 13, 14, 1948.

STANDARDIZATION PROCEDURE FOR DETERMINATION OF AEROSOL DELIVERY OF NEBULIZERS BY PHENOLSULFONPHTHALEIN AEROSOLS

Preliminary Report

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THE number of commercially available nebulizers for aerosol therapy of the lungs is increasing daily. Often exaggerated claims are made, both by the manufacturer and by the physician. It appears timely to propose that nebulizers be *certified* by the manufacturer to be capable of delivering a specified quantity of aerosol (not liquid) under standard operating conditions. In continuation of previous experiments we now propose the following procedure for the standardization and certification of nebulizers.[1]

1. Into the dry nebulizer, pipette 2 c.c. of 0.1 per cent phenolsulfonphthalein (PSP). Place small rubber stopper in air vent (if present) and attach the standard L-tube (DeVilbiss 640 L-tube), which acts as a one stage baffle, to mouth of nebulizer so that the L-tube is parallel to the table top.

2. Connect nebulizer to oxygen tank, or any suitable compressed gas with pressure tubing, and turn on oxygen. The tank is equipped with a gauge graduated in liters per minute. The time is counted from the moment the gauge reaches the required volume velocity, i.e., 8 1/m, et cetera, depending upon the construction of the nebulizer used. It is understood that this is an uncorrected volume velocity. A correction is not necessary for our present purpose.

3. After the gas has been allowed to run through for the desired time, usually five minutes, disconnect the rubber tubing from the nebulizer. Remove L-tube and wash out completely into a 50 c.c. volumetric flask, add 5 c.c. of 5 per cent NaOH. Bring volume up to 50 c.c. Determine colorimetrically.

4. The nebulizer is now washed out completely into a 500 c.c. volumetric flask. Five c.c. of 5 per cent NaOH is added, the volume brought to 500 c.c. and determined as for the L-tube.

From the Biological Laboratory, Cold Spring Harbor, New York, and the First Medical Service, and Laboratories of the Mount Sinai Hospital, New York City.

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TABLE I

RESULTS OF TYPICAL EXPERIMENTS ON NEBULIZER STANDARDIZATION

All nebulizers in this group were operated for 5 minutes with stopper and L-tube

	1 Mg. Dye per c.c.	2 Type of Nebulizer	3 Initial Volume of PSP in c.c.	4 (Uncorrected) Volume Velocity of O_2 in L/m.	5 Residue in Nebulizer in mg.	6 Total Delivered in mg.	7 Baffled Quantity by L-tube in mg.	8 Per Cent Delivered	9 Ratio of Col. 7 to Col. 6 Per Cent
1.	1.04	DeVilbiss No. 40 (1)	2	6	1.43	0.65	0.13	31	20
2.	1.04	DeVilbiss No. 40 (2)	2	6	1.40	0.68	0.11	33	16
3.	1.03	DeVilbiss No. 40 (3)	2	6	1.30	0.76	0.13	37	17
4.	1.07	Vaponephrin (1)	2	5	1.34	0.80	0.004	37	0.5
5.	1.07	Parke-Davis Table Model	2	5	1.95	0.19	0.005	9	2.6
6.	1.07	DeVilbiss No. 44	2	4	1.97	0.17	0.00	8	0.0

The foregoing gives the following information:

1. Residue of dye in nebulizer itself.

2. Dye baffled out of L-tube. This is a rough value of "rain" plus larger particles subtracted from the original quantity by the nebulizer in addition to the L-tube deposit.

3. The initial quantity of dye in the nebulizer, minus the residue in the nebulizer, gives the total dye delivered by the nebulizer. This fraction holds in general for any solid dissolved substance.

The dye in the L-tube is a rough measure of the number of larger particles delivered. It is believed that the ratio:

$$\frac{\text{Dye in L-tube} \times 100}{\text{Total dye delivered}}$$

should not be greater than 35 per cent. However, the clinical importance of this ratio has not as yet been evaluated.

The important point emphasized by this report is that *aerosol delivery should be certified by the manufacturer of the nebulizers and that claims should be supported by acceptable laboratory evidence.*

Table I illustrates results obtained with this technique on four commercially available nebulizers. It should be emphasized that these data do not indicate in any fashion whatsoever which nebulizer is "the best" nebulizer. Sufficient data are not available to determine what particle size distribution is most desirable. The procedure and the table are designed to illustrate the way in which nebulizer delivery may be studied and standardized. Of the four nebulizers given in the table as examples, it is evident that the DeVilbiss No. 40 and the Vaponephrine nebulizers deliver sufficient mist to warrant their use with both epinephrine and penicillin under our conditions. On the other hand, there are many factors, which will be discussed in detail in a future communication, which determine, in

any particlular case, which nebulizer is to be preferred for clinical application. There are always restrictions attendant upon the use of certain nebulizers, e.g., where high volume velocities are involved. Certain nebulizers, for example, cannot be used efficiently with high volume velocities which are desirable with nasal tips. Other nebulizers are very efficient with low volume velocities. It has been pointed out previously that 10 liters per minute is desirable with nasal tips. In addition, the particle size distribution, as determined by the quantity baffled by the L-tube (Column 7), makes it appear likely that wider range of particle distribution, and thus clinical effectiveness, might be made available by nebulizers which provide from 10 to 50 per cent of the mist delivered in particles large enough to be baffled by the L-tube.

Comparison of dye and penicillin aerosol excretion in man are experiments now in progress.

SUMMARY

By nebulizing a solution of a standard dye, under specific conditions, the quantitative delivery of aerosols by commercial nebulizers may be readily determined. It is recommended that commercial nebulizers be certified as to aerosol delivery by the manufacturer.

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THE USE OF ORAL POTASSIUM TREATMENT IN ATOPIC DERMATITIS

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THIS report is based on the clinical observation that a number of patients presenting the syndromes of both bronchial asthma and atopic eczema showed improvement of the dermatological condition when given potassium iodide orally for the chest symptoms; a group of patients with typical atopic eczema alone was so treated. Each was given a saturated solution of potassium iodide by mouth; and no other treatment, topical or otherwise, was instituted. In three patients who were hospitalized for this study, immediate marked improvement occurred. Change of environment may have played some part, although one individual has maintained his complete remission while at home. One patient, not hospitalized and given no other treatment, has been in remission for fourteen months.

The study is being extended to a public clinic and to the laboratory in order to establish such causal relationship as may be present.

A STUDY OF ONE HUNDRED ALLERGIC INDIVIDUALS BY THE MINNESOTA MULTIPHASIC PERSONALITY INVENTORY TEST

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ONE hundred patients, seen in a public allergy clinic, were studied by means of the Minnesota Multiphasic Personality Inventory Test. The allergic syndromes were limited to hay fever, bronchial asthma, or both.

Eleven patients demonstrated hypochondriasis. In one of these, the personality trait was associated with hysteria and in two others there were, as well, traits of hysteria and also depression. In one, the hypochondriasis was associated with traits of sexual inversion. Five female patients presented high scores for masculinity; and one male, a high score for femininity. Four patients showed marked scores for depression and five for hysteria. Two demonstrated psychasthenia, one schizophrenia, and one hypomania. Fully one third of the patients were obviously psychoneurotic.

AN EVALUATION OF ROUTINE X-RAY STUDIES IN ASTHMATIC PATIENTS

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ROUTINE chest and sinus x-rays were done on 450 consecutive patients presenting bronchial asthma as their chief symptom. Of the 220 completely evaluated, approximately thirty showed both systems to be normal. Of the others, fifty-six presented mild emphysema, which was moderate in an additional 104, and marked in thirty-three. Evidence of bronchitis was mild in ninety-four, moderate in eighty-four, and marked in nineteen. Hilus shadows were slight in eighty-one, moderate in eighty-six, and marked in twenty-two. Thickened sinus membranes were reported slight in eighty-nine, moderate in fifty-six, and marked in forty-four.

For other conditions, tuberculosis was present in sixteen, bronchiectasis in nine, atelectatic patches, four; emphysematous blebs, two; cervical ribs, three; tracheal deviation, sixteen; enlarged left ventricle, five; and sclerotic aorta, sixteen. Other pathological conditions were present in very small numbers. In nineteen patients polypi were diagnosed by x-ray. Incidental diagnostic findings were: three patients with neoplasms and three with Paget's disease.

The final report will be presented when a total of 500 patients similarly studied has been evaluated.

A DURHAM-TYPE AIR-SAMPLING DEVICE FOR LESS THAN ONE DOLLAR

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Flint, Michigan

THE stainless steel air-sampling device as described by O. C. Durham (J. Allergy, 17:79, 1946) costs in the neighborhood of $20.00. A simple, equally effective air-sampling device (Fig. 1) can be made by the use of

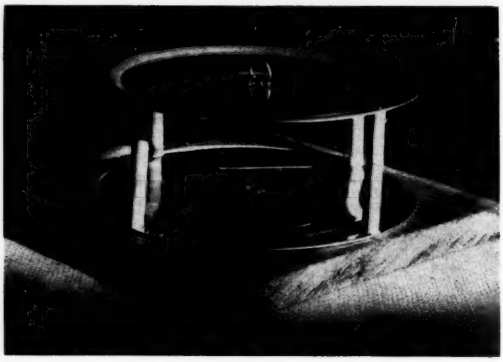

Fig. 1. Inexpensive Durham-type air-sampling device.

two aluminum pot lids, four pieces of ½ inch diameter doweling for posts, and a wall hook bent to serve as a slide holder. A crate end or any piece of board can serve as a base.

Cost of materials: slightly less than one dollar.

Construction time: forty-five minutes to one hour.

AEROSOL PENICILLIN IN ALLERGIC PATIENTS WITH RESPIRATORY INFECTIONS

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AEROSOL penicillin was administered as an adjuvant therapeutic office measure in the ambulatory management of allergic patients with acute and chronic diseases of the upper and lower respiratory tracts.

Over 200 aerosol treatments were given to seventy-nine patients with respiratory allergies, complicated by secondary infection of the respiratory tract. In forty-two of these patients, the underlying major allergy was bronchial asthma; eight patients had hay fever, and twenty-nine had allergic rhinitis.

Description of the technique employed is included.

Emphasis is made of the simple and readily adaptable procedure in all age groups, the paucity of side effects, and its possible role in limiting the course of secondary respiratory infections in allergic patients.

Also included is a table of the patients receiving the treatment, showing the effect of aerosol penicillin on the vital capacity, sedimentation rate, et cetera.

It is felt that the presentation of additional clinical data is desirable pertaining to the use of aerosol penicillin in allergic patients.

COCCIDIOIDOMYCOSIS TREATMENT WITH HISTAMINE

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COCCIDIOIDOMYCOSIS was first described in 1892. In 1937 it received recognition as being endemic in certain areas of California, Arizona, Texas and possibly a few other dry climates, caused by the diphasic fungus coccidioides immitis. There are two types: (1) simple or initial, (2) progressive, secondary, disseminating—usually fatal. One case in 500 is of the disseminating type, known as coccidioidal granuloma. The condition produces a high metabolic rate, eosinophilia, and other allergic symptoms —especially those produced by large amounts of histamine or histamine-like substances. Treatment has been immunologic therapy. Histamine was used intravenously and subcutaneously, in one case, to build up histamine tolerance with rapid subsiding of clinical symptoms and apparent cure. There is no record in the literature of histamine's being given intravenously in a case of progressive coccidioidomycosis before.

MASSIVE SPONTANEOUS SUBCUTANEOUS EMPHYSEMA OCCURRING IN AN ASTHMATIC ATTACK

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THE spontaneous occurrence of subcutaneous emphysema is an uncommon phenomenon. A review of the literature reveals only twenty-one previously reported cases, of which several had a concomitant pneumothorax.

The two cases reported in this paper occurred in young, vigorous males who had been having infrequent attacks of asthma for several years.

In both cases there were no warning signs or symptoms. During an acute asthmatic siezure, the patients noted puffiness of the neck which cracked on palpation. In one instance this swelling extended over the entire right chest and abdomen down to the inguinal ligament. During

treatment, consideration was given to multiple skin punctures and insertion of drains. However, in neither case was the patient excessively dyspneic; and, as both patients responded to conservative measures, they were treated expectantly. The emphysema absorbed completely in both instances, in ten and fourteen days.

An interesting feature about one of these cases is the path taken by the air from the ruptured vesicle in the peripheral lung, along the walls of the bronchioles and the blood vessels, into the middle mediastinum—causing a shift of the heart to the left—thence along the facial planes to the neck, and finally subcutaneously down the chest and abdomen to the inguinal ligament.

Spontaneous subcutaneous emphysema may occur more frequently than reported, but because the syndrome is asymptomatic it is probably overlooked.

"CEREBRAL EDEMA" DUE TO PHENOBARBITAL SENSITIVITY

(Continued from Page 349)

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Progress in Allergy

BRONCHIAL ASTHMA V

Critical Review of Literature

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We have again attempted to cover the literature on asthma and related conditions, this time from July 1, 1947 to September 30, 1948. In addition, a few articles of earlier dates are included because they were not mentioned in our first four reviews of the literature of 1943,[518] 1944,[519] 1945,[520] and 1946-June 30, 1947.[521]

Antihistaminic drugs are increasing in number, with many articles. A healthy sign, too, is a revival of the study of physiological and pharmacological aspects of the respiratory tract. Psychological factors seem to draw more and more attention. Reports from military sources are now very few.

The study of allergy has spread to many countries. Allergy societies continue to increase in this country and many new ones have been formed in other countries. This increased popularity has stimulated a large number of articles written in foreign languages. We have been fortunate in obtaining expert assistance in studying many of these, and we here wish to acknowledge, with gratitude, help received from Drs. Carlos Tanturi (Argentina), Gonza Estrada De La Riva, (Havana, Cuba), Jacques Sclafer (Paris, France), and Arnold Schimberg and H. Blackburn (Chicago). Once again we beg those who write in languages other than English to end their articles with a summary in English. This summary should not merely discuss the subject matter; it should give facts and figures wherever possible. In return, those of us who write in English should reciprocate. We again ask for reprints on asthma and related subjects, with translations or abstracts of all foreign papers, so that we can include them in our next review.

NEW BOOKS

New books have been few and none deal with asthma alone. "Synopsis of Allergy," by Alexander,[16] second edition, presents the essentials of allergy in a compact form, and includes excellent chapters on bronchial asthma, allergic dermatoses, and allergy to drugs and chemicals. Drawbacks exist, e.g., the belittling of skin tests and the complete acceptance of the unproved theory that contact between a specific antibody "and the atopen causes the release of histamine (H-substance)."

Another second edition is on "Physiologic Therapy in Respiratory Diseases." Barach has done well and "correlates the pathologic physiology of each disease entity with the physiologic principles which underlie the treatment of the condition by inhalation therapy and other procedures which have value in the management of respiratory diseases."[49]

Black's revision of Vaughan's "Practice of Allergy" is a "must" in this field. However, as stated in a review, the book remains Vaughan's, for the most part, with relatively little new information by the new author, and with only a few recent references in spite of many new articles and books on the subject.[533]

"Office Immunology Including Allergy," by Sulzberger and Baer, along with four other authors, is excellent, although, as expected, there is much more discussion of dermatologic allergy than that of the respiratory tract.[500]

Kern[279] has a book on "Perennial Allergic Rhinitis: the Most Important Respiratory Allergy."

Forman[161] has compiled a very useful "Directory of Physicians Interested in Clinical Allergy." The names are listed by states, cities and countries, with brief data concerning membership in professional societies.

We recommend four books on fungi. They are Henrici's "Molds, Yeasts and Actinomycetes" (second edition and revised by Skinner, Emmons and Tsuchiya);[252] Nickerson's "Biology of Pathogenic Fungi";[359] "Fungi of Manitoba and Saskatchewan" by Bisby and others;[66] and "The Fungi" by Wolf and Wolf.[563]

ETIOLOGY OF BRONCHIAL ASTHMA

Alford[18] has an interesting paper on allergy in Japan. In contrast to the United States, grasses and ragweeds are unimportant; hyposensitization is practiced only in

the medical schools. All sorts of nonspecific measures are used, some good, some useless. There are no active allergy clinics. House dust is of little importance in Japan because "a typical Japanese living room has no drapes, rugs, pillows, upholstered furniture or animal pets. These rooms thus approach our concept of a dust-free environment. The bedrooms do not have beds or mattresses. Cotton quilts are placed on the floor and the small pillows are frequently of straw. During the daytime these quilts are folded up and placed in bureau drawers or cupboards. There is usually considerable air circulating through the houses due to their construction and thus house dust cannot accumulate easily." Asthma does occur in Japan, with one case due to inhalation of silk worm cocoon, and others to various foods and especially to Ascaris infestation. As in South America, sensitivity to foods seems much more important than to inhalants, although mold allergy is frequent. Urticaria, especially to various sea foods, is the most common allergic condition in Japan. The Japanese are not racially immune to hay fever even though hay fever does not seem to exist in Japan.

In Norway about 700 persons are totally disabled as a result of bronchial asthma. Claussen[116] surveyed 86 of the 377 districts. There were 1,190 asthmatic persons among the 295,356 inhabitants in those districts. From these figures, he estimates at least 12,000 persons with asthma in all Norway (population about three million). Like other observers he found more male patients (58 per cent). In the first decade there were only thirty-four girls to every sixty-six boys, and in the second decade boys constituted 69 per cent. In over fifty cases the asthma had lasted over forty-five years. There was no great difference in the frequency of asthma in coastal and interior districts. Complete disability occurred in 7.3 per cent of the men with an average age of fifty-three years and an average duration of the disease of eighteen years. Only 4.5 per cent of the women were completely invalided. The family history was positive in 50 per cent, with onset of asthma earlier in those with positive history. Asthma is a national scourge.

POLLEN

Pollen as a cause of hay fever and asthma continues to draw attention. By using two simple sampling devices Durham tested the allergen-producing ability of more than sixty plant species and several fungi. As a result of repeated spot testing of the air in the immediate vicinity of single plants, small plots or extensive acreages, he obtained some extraordinarily high counts, especially high when compared with maximum gravity data (stated on volumetric basis), as previously reported for these plants in areas where they are most abundant. For example, a spot count of 9,600,000 ragweed pollen was found in a visible cloud twenty feet from the weeds themselves. Other high spot counts were 160,000 for burweed marsh elder (iva xanthiifolia), 2,000,000 orchard grass, 460,800 Canada blue grass, and 328,000 redtop.[103] Such extreme figures emphasize the fact that occasionally one or a few plants can cause hay fever or asthma in a person who happens to be close by.

Durham[103] found that some of our National Parks are entirely ragweed-free; some contain ragweed in season, e.g. near Mammoth Cave, Kentucky. Durham and his collaborators of the American Academy of Allergy[104] give the 1947 ragweed pollen counts from fifty-eight different locations in various parts of the country. The totals range from nine in Grand Canyon, Arizona, to the high counts customary in the midwest, especially in Decatur and Peoria, Illinois. Walzer and his co-workers[650] surveyed New York City and its metropolitan area. In 1946 the seasonal pollen totals were uniformly low; that for Brooklyn was only 48 per cent of the average for the past eleven years. During this same year totals for Washington, D. C., Philadelphia and Cleveland were two to five times the average total for New York City.

Stroh,[499] in the Northwest, states that the Cascade Mountain range divides this area into two distinct regions with different climates and pollens. West of this range the weather is similar from Northern California to Juneau, Alaska, with tree pollen in February and March. Grasses begin in April and reach their maximum in June. There is no true fall season. East of the range the flora is typically midwestern with slightly later tree and grass seasons; the fall season is most important (Russian thistle and sagebrush, especially).

Ordman,[305] in South Africa, found that symptoms occurring in the summer are almost invariably due to grass pollen (October to March.) Tree pollenosis is uncommon, but hay fever in spring and winter is usually due to the pollen of the Cypress tree. Weeds are of little significance though *Compositae* (especially common garden flowers) can cause symptoms. Alemany-Vall[12] found grasses most important—there are ninety-seven species within the municipal boundaries of Barcelona, Spain, from March to July; the pollen of *Parietaria Officinalis* is a frequent cause of simple and complicated rhinitis and asthma.

Veldee[355] discusses the qualifications of the pollen collector, the labeling and type of containers, the purity and stability of the pollen, change of color in dried pollen, and the necessary co-operation between the user and the collector of the pollen. The New York City Health Department destroyed more than 1,000 acres of ragweed by spraying with a chemical which kills the weed before pollen is set free.[357] Ragweed hay fever does not occur in Europe, although a few ragweeds are found in local areas.[33] Filters protect against pollen hay fever but those whose asthma is due to pollen usually do not clear up until they have been in an air-filtered room for from one to several days.[24]

FUNGI

The role of fungi as a cause of rhinitis and asthma is now well established. Durham[165] did counts of both fungi and pollens. His highest natural Alternaria count was 13,600 in Illinois, but from a heavy cloud of dust produced by an operating combine he obtained spot counts of 675,000 Alternaria, 869,000 Hormodendrum, and 177,327 Helminthosporium. In another spot count he found 500,000 corn smut. These terrific figures prove what we have known clinically and by skin tests—that certain molds and smuts can and do cause respiratory symptoms in many individuals.

Eisenstadt,[172] in a study of 380 cases of respiratory allergy, ages two to sixty-four, tested with eight different 1:1000 mold extracts. Positive reactions were obtained in 129 cases (34 per cent.) Inhalation of one or more molds was the main cause of the respiratory allergy in forty-two patients (11 per cent), and a contributory factor in another sixty-nine cases (18 per cent)—total 29 per cent. Alternaria and Hormodendrum were of major importance, both in relation to mold spore counts and to frequency of positive skin tests. Other molds may also be of clinical significance, and the author rightly urges routine testing with mold extracts in all patients with asthma and rhinitis, including hay fever. On two occasions constitutional reactions occurred after intradermal testing. [These reactions which could have been serious, even fatal, emphasize the necessity for doing preliminary skin tests by the scratch method. Besides, scratch positive reactions with mold extracts are almost always associated with clinical sensitivity. This is by no means true with the intradermal technique. Eisenstadt, for example, in this paper obtained positive intradermal skin tests to molds in eighteen patients in whom there was no clinical significance].

Morrow[350] made another survey of thirty-one stations in the United States for periods up to six years. By the mold culture plate technique the following molds were the "top ten:" Alternaria, Hormodendrum, Penicillium, Aspergillus, Pullularia, a sterile pale species, sterile dark species, Torula, Fusarium, and Trichoderma. In January and March by the plate method only, Newton, Scherago and Weaver surveyed parts of Kentucky. Penicillium was the most prevalent mold in all parts of the state. They found four genera, *Montospora, Stemphylium, Tetraccocosporium,* and *Phycomyces,* not previously reported in Kentucky. Certain molds predominated in outdoor air and others in house dust; mold surveys should therefore include house dust as well as outdoor air.[358]

From West Texas, in a five-year survey, Sellers and McKenzie[456] made intradermal tests with eight mold extracts in 392 sufferers from inhalant allergy. Thirty-three patients (8.4 per cent gave positive tests only to molds, and another 141 (35.9 per cent) were positive for molds and other inhalants. Mold sensitivity was especially common in patients under twenty. Specific treatment was successful in twenty-one of the thirty-three patients sensitive only to molds and in 49.4 per cent of those patients who were allergic to molds and other inhalants. Molds are present throughout the year in the Abilene area of Texas (slides and plates).

From Copenhagen, Denmark, Flensborg and Samsoe-Jensen[188] surveyed the outside air from March to September, 1947: the mold spore counts were very high, especially during the summer; Hormodendrum was most important, especially in and after June, reaching 80-120 colonies daily most of this time, with a peak of 260 one week in July. This mold accounted for 72.4 per cent of all molds, with Penicillium 9.2 per cent, Monilia 2.4 per cent, Pullularia 2.2 per cent, and Alternaria 2 per cent. In a study of the homes a different situation was found—various species of Penicillium were present and only occasionally Hormodendrum. In discussing this paper, Nilsby, from Sweden, agreed that Hormodendrum was far more prevalent than Penicillium in outdoor air, but Penicillium was found indoors in 43.5 per cent, Hormodendrum in 27.5 per cent, Yeast-like structures in 10 per cent, Aspergillus in 6.2 per cent, and Alternaria in 2.1 per cent. Molds may differ in different homes. In one home, there was a pure culture (25 colonies) of Alternaria, a mold rather rare in Sweden. Schwartz of Copenhagen cultured the house dust of twenty-two asthmatic patients (plate exposures). He found a total of 239 fungi with a great predominance of

Penicillium, followed by Aspergilli, Mucor and the others. In one home there were seven different varieties of Penicillium yet only one of these gave a good intradermal test on the patient.

Two methods of preventing mold growth on books are offered. One is to maintain humidity below 75 per cent in a book case by open bags containing silicagel, the other by wiping the bindings with a solution containing thymol, mercury bichloride, ether and benzene.[130] Cavallero has a long review of allergic diseases due to fungi.[306]

Dutton[167] believes that a patient can be sensitive to fungi present in his own bronchi. For twelve years he has studied sputum of asthmatic patients, both by the usual stains and by culture. In a small percentage, non-pathogenic fungi of various kinds have been found and extracts of these fungi have given excellent scratch, intradermal, and transfer reactions in some of these patients, with clinical improvement by hyposensitization. By this technique a small but significant number of patients has been definitely benefited. A few in this group showed no other sensitivity nor other factors to explain their asthma, and for them the results have been striking.

HOUSE DUST

Three excellent papers come from a group in London. Rimington, Stillwell and Maunsell[418] obtain their dust for extraction from a single dust supply, chiefly from carpets. The crude house dust extract is prepared by soaking in ammonia, squeezing out the extract, followed by re-extraction and filtering through Kieselguhr. The completed extract contains 2-3 per cent nitrogen and is used for testing in a 1 per cent solution. The authors state that their method gives stronger intradermal reactions in house dust-sensitive patients than do Seitz-filtered fractions. In the second paper[497] the authors compared the reactions given by allergic individuals to purified house dust antigens, the pooled extracts of twenty-six strains of molds grown in pure cultures, the culture fluid obtained from the latter, and materials predominately polysaccharide in character isolated from four species of Penicillium and one species of Caldariomyces. All these mold extracts gave negative intradermal tests in nonallergic persons. In sixty-two patients with allergic rhinitis, tests for the house dust extract were positive in forty-five; of these, fifteen were also positive for the mold extracts. All seventeen patients who were skin-negative for dust were also skin-negative for molds; no patient showed a sensitivity to molds and an insensitivity for house dust. There was a striking chemical similarity between the three polysaccharide products derived from the molds after hydrolysis and the dust antigen. All showed polypeptide-like grouping of simple amino acids associated with a polysaccharide complex. The usual color reactions for protein were not obtained.

In the third paper[366] their crude dust antigen (10 mg. to 10 cc. normal saline plus 0.5 per cent phenol) was diluted serially to 10^{-4}, 10^{-5}, and 10^{-6} concentrations. Of forty-nine nonallergic persons none gave threshold reactions with the 10^{-6} dilution, three reacted to 10^{-5}, and seventeen to 10^{-4}. Negative reactions were obtained in twenty-nine (58 per cent) of normals to 10^{-4}, whereas 90 per cent of ten persons with a history of allergy reacted to this dilution, and four of these to 10^{-6}. Positive tests to 10^{-5} were obtained in fifty-five of eighty allergic patients. In a group of thirty-five positive-dust-reactors twenty-two also gave positive tests to extracts of cats, feathers and/or molds. No patient reacted to one of these latter three and failed to give a positive test for house dust extract. After hyposensitization there was a decrease of the threshold reactivity to the dust extract but a blocking antibody was not found in the blood of those patients. [The authors could have obtained a much stronger dust extract by discarding rug and carpet dust; dust from bedding and soft furniture is much more potent.]

That molds are important in house dust, but not the entire story, has also been shown by Reymann and Schwartz.[410] (Also see discussion above of paper by Flensborg.) From the dust obtained from the homes of twenty-two asthmatic patients, 239 fungi were cultured and six of these patients gave positive skin tests to those molds when extracted. Those who were mold-sensitive also gave positive skin tests for house dust but the reverse was not always true. Of these twenty-two patients thirteen gave positive tests for their "autogenous" house dust extract, and five of these also gave positive skin tests for the fungi present in their own dust. Blamoutier[72] discusses the house dust problem as a cause of asthma and the origin and nature of the dust. He is very skeptical as to results of specific hyposensitization. [This skepticism is not shared by most American allergists. We know that we obtain excellent results in most cases of dust-sensitive respiratory allergy; we combine rigid elimination of inhalation plus hyposensitization. We admit that we do not know what per cent of improvement is due to the injections alone, but, by analogy with results in those who receive injections of extracts of horse dander, molds and pollens, we feel

that hyposensitization is an important and useful procedure, and we therefore do not share his skepticism.] An answer to a query[25] correctly states that "generally a stock dust preparation made by obtaining house dust from a number of homes, preferably of patients with respiratory allergy, is satisfactory in the majority of cases of sensitivity to house dust. There are occasional patients in whom a preparation made from the dust of the individual's own home ("autogenous") gives better reactions than the stock dust preparation. This may be due to a relatively excessive amount of one or more of the allergens in the preparation to which the patient is selectively more sensitive," e.g. feathers or kapok. [It should also be pointed out that, as stated above, a particular house dust may contain one or more molds to which a patient may be specifically allergic.]

INHALATION OF FLOUR AND GRAIN MILL DUSTS

Jiménez-Díaz and his associates[272] from Madrid confirm previous reports that cereal dust contains more than one ingredient. In order of importance they place fungi, insects, acarina, and substances in the dust and flour itself. The most important fungi are rusts, smuts and Tilletia; these are found in great quantities in granary dust and that of milling establishments, owing to their fineness and the ease with which they spread once the covering of the invaded grain has been broken. The infected grain, equally with Ustilago and Puccinia, can spread in the air when the seeds fall and may affect neighboring people. Other fungi, e.g. Aspergillus and Penicillium, can invade damp flour, but much less often. Cases are noted of sensitivity to tricoptera (Caddis fly,) ephemerida, Musca domestica, and Climex lectularius. Coleoptera can cause symptoms in mill workers or in those close by, while sensitization to the flour itself is of most importance in bakers. In twenty-four cases, especially with sensitivity to Tilletia (main cause of asthma in mill workers and others exposed to grain in Spain,) positive skin tests were obtained and positive passive transfer in fourteen Tilletia cases. On the other hand, only two positive transfer reactions were found to the flour itself.

Four other papers discuss allergy in bakers. Linko[302] from Finland, examined 328 workers and found sixty-six (20 per cent) with clinical allergy to flour. Forty had only nasal symptoms, twenty both nasal and asthmatic trouble, and only six asthma alone. Blood eosinophilia was found in nineteen, with positive skin tests to cereal extracts in 60 per cent. Family predisposition did not seem important. Onset of symptoms averaged eleven years after entering the profession, with earlier onset in thirty-two cases. Schwartz, from Copenhagen, found thirty-five persons with flour allergy (twenty-four bakers, two millers, seven confectioners, one worker in a biscuit factory, and a miller's son.)[448] The average sensitization time was under eleven years. Specific desensitization with flour extracts led to improvement in only 38 per cent of cases. Schwartz has an excellent discussion of flour allergy; it is an occupational disease and therefore prophylaxis is important. This includes (a) lessening of the amount of dust in bakery shops by better ventilation; (b) avoidance of this occupation by allergic individuals; and (c) he points out that some bakers can become confectioners because of less flour dust. In Denmark for the period 1928-42, inclusive, 1,654 persons received an invalid pension because of asthma; of these only fifteen were bakers, confectioners or millers, a very low percentage. Eight of the above thirty-five patients quit bakery work, seven of these had not been helped by hyposensitization.) Seven of these men became symptom-free within three months but all receive lower wages in other trades. One is disabled with bronchiectasis. It is interesting to note that these flours were examined microscopically and were free from mites and other insects, and that injections were given for from six weeks up to four months. [This confirms our impression of the difficulty in clearing baker's asthma while the patient remains exposed to large amounts of flour. Housewives are less exposed and usually get excellent results even when they inhale some flour dust at intervals.]

Alemany-Vall (Madrid)[11] also discusses asthma and rhinitis due to flour. The appearance of eosinophilia in the nasal or bronchial secretions seems to be a prelude to attacks. From South Africa, Ordman[367] says that wheat was recently lacking, and various flours, especially cassava and buckwheat, were added to the usual wheat flour in the manufacture of bread or even used alone in confectionery. Cassava, (arrowroot) and in the granulated form called tapioca, has never been incriminated, and Ordman, too, was unable to prove the case against this food. But buckwheat has been repeatedly found to be an offender, and in three bakers and confectioners asthma and coryza followed inhalation of buckwheat flour; in two symptoms also occurred after eating baked buckwheat products. Skin tests were strongly positive by the scratch method, confirmed by intradermal tests, but reactions were not as large as expected from the literature. Hyposensitization was attempted but results were doubtful.

FOODS AS A CAUSE OF ASTHMA

There has always been much discussion as to the proportionate role of foods in asthma. Foods can and do cause attacks, but usually dramatic episodes from certain foods are infrequent and are usually due to such foods as egg, nuts and fish. The great question is the possible hidden, less dramatic, role of foods in causing more or less chronic asthma and rhinitis. This question would not be necessary if we could rely on our skin tests, but it is usually only in the relatively few dramatic cases that food-skin tests are accurate, and coincide with the history. Opinions range from those of Rowe, Randolph and Rinkel who are strong food-allergy advocates to those of many allergists who believe that asthma and rhinitis from foods is rare.

Hill studied food sensitivity in 100 asthmatic children,[259] ages three to twelve. Thirty-five of these children gave positive scratch tests for one or more foods; in sixty-five the tests for foods were entirely negative. Hill did not try food-intradermal tests as he feels that this method is not reliable. (He states, however, that the intradermal tests for inhalant allergens are very valuable and usually are clinically important even when scratch inhalant tests are negative.) If these asthmatic children had remissions of three to four weeks, foods were not the cause of asthma, says Hill. But, if symptoms were continuous, foods were removed from the diet and reintroduced one at a time during asthma-free intervals (except with such dangerous and known causes as fish or nuts in particular cases.) Attacks had been or could be induced by specific foods in twenty-four cases, but in most of these the parents knew the offending foods and already avoided them. There were 218 positive scratch tests in the 100 children and forty-four of these tests (20 per cent) were clinically corroborated as causes of asthma. Egg white, fish, peanut, walnut, and chocolate comprised thirty-eight of these forty-four, with tomato a cause in two cases, and one each for spinach, orange, corn and barley. Despite positive tests for potato in twenty-two cases, Hill was never able to prove that potato caused asthma, and while spinach gave many positive tests, ingestion caused asthma in only one child. In sixteen cases (8 per cent) a food which gave a positive test caused irritation about the mouth, vomiting, urticaria, or angioneurotic edema, but not asthma (asparagus 1, banana 1, egg white 4, fish 2, orange 1, peanut 1, spinach 2, walnut 2). In 158 positive food tests ingestion did not cause symptoms; perhaps the child did not eat enough of that food.

Hill suggests that positive tests for foods may have the same significance as a positive tuberculin test, causing a positive reaction which may or may not have anything to do with the clinical condition, but may represent past sensitivity. Hill concludes that (1) 20 per cent of positive scratch tests for foods are etiologically significant in asthmatic children; (2) parents usually know which foods cause asthma and have already avoided them; (3) the most important foods are fish, egg, walnut, peanut and chocolate; (4) wheat and milk can cause asthma in children but are uncommon causes; and (5) food sensitivity is important in asthmatic children but less so than is sensitivity to inhalants. [Hill finds chocolate important; we rarely find this a factor in asthma, although important in migraine.]

Rowe and Rowe[429] disagree with Hill and others. In 411 children with asthma (up to twelve) foods were the sole cause in 50 per cent of the younger children (up to five), and along with inhalants responsible for another 38 per cent. In the older group (five to twelve) foods were the sole cause in 26 per cent, being associated with inhalant allergens in another 53 per cent. Inhalant allergy of all types was a major or secondary cause in 58 per cent of the younger group and in 71 per cent of the older. Foods were therefore more important factors in infancy but always remain important. Rowe and Rowe also attest to the unreliability of intracutaneous-food tests, and they feel that most people who have "colds and bronchial colds" which recur every two to eight weeks, especially from early fall to late spring, are really allergic, especially to foods. Respiratory infections are rarely responsible, and bacterial allergy rarely causes asthma. Of the inhalants pollens are much more important than animal emanations, house dust, fungi, or miscellaneous substances. They stress their standardized cereal-, egg-, milk-free diets as aids in the detection of food allergy.

In asthma in patients over fifty-five, Rowe and Rowe[430] again emphasize the importance of foods in etiology and their belief that bacterial allergy is of little importance. Food and inhalant factors were about equally responsible for the asthma in their patients. The recognition of the importance of foods depended chiefly on the routine use of their standard elimination diet. Clinical food allergy rarely could be demonstrated by skin tests. (The authors also discuss the management of those allergic to inhalants.)

Their report is based on 173 private patients over fifty-five who obtained good to excellent results from 1940 to 1946—none under treatment less than six months. The onset of asthma occurred after the age of fifty-five in fifty-one

patients, and between fifty and fifty-five in twenty-one more. The duration of asthma ranged from less than a year in twenty-two cases to over twenty years in thirty-eight. Asthma was perennial in 129, and recurrent exaggerations or attacks occurred in eighty. Other manifestations of allergy occurred, e.g., perennial nasal allergy in ninety-seven, and seasonal in thirty-three. There was a positive family history of asthma in eighty-one cases and of nasal allergy in eighteen.

As regards skin tests (they use the scratch technique with foods, scratch and intradermal with inhalants), Rowe and Rowe state that although skin tests were entirely negative in seventy-three of the 173 patients, fifty-eight were proved allergic only to foods, eleven to pollens and foods, and four to pollen alone—thus demonstrating the fallibility of skin tests in determining food allergy and, to a lesser extent, of inhalant allergy. In the 100 patients who gave positive skin tests grass pollen was positive in sixty-two, fall in fifty-three, tree in fifty, flowers in forty-five, animal emanations in forty, miscellaneous inhalants in forty, house dust in thirty-nine, fungi in eighteen, and foods in thirty-one.

[One can only comment that (a) these reports and that of Hill are at variance. Perhaps the routine use by Rowe of his elimination diets and the care with which his long experience has equipped him may well be the answer. No one believes that there is a great deal of difference in inhalant and bacterial environments between Oakland, California, and other parts of the country. (b) On the other hand, we are at a loss to explain the small number of reactions to house dust and fungi in Rowe's two papers. Perhaps if he used a potent dust extract, e.g. Endo's, his dust-positive cases would increase in number.] That care as regards foods is important is stressed by Rowe in his attention to details about the diet and his insistence that good results require (a) absolute adherence to the diet, (b) frequent conferences with the physician to detect willful or unintentional errors, and (c) realization that relief will appear in 2-14 days, depending on the time the allergens of formerly-eaten foods remain in the body and the time required for the lung cells to recover from allergic reactions. On his elimination diets sixty of the 173 patients gained weight, with no change in sixty-seven, desired loss of weight in twenty, and undesired loss, moderate in degree, in only ten.

Randolph[407] also has a long article on food allergy. Recognition of food allergy is obscured by several prevalent misconceptions. The facts are, he states, that (a) food sensitivity is as common in adults as in children; (b) patient's opinions of foods responsible are usually wrong when dealing with substances frequently ingested; (c) skin reactions to food extracts are unreliable and misleading guides for diet control; (d) any food may act as an allergen and expected incidence of allergic response is directly related to frequency of ingestion; and (e) inhalant sensitivity coexistent with food allergy should be treated before investigating the role of foods. Randolph discusses his method of food investigation which includes test meals with total leukocyte counts before and twenty, forty, and sixty minutes after the initial feeding. He has very clear tables and diagrams and he illustrates the cyclic aspects of food allergy. Corn is his chief offender, followed closely by wheat, milk, egg, potato, orange, beans, and other foods.

[From a study of such articles on food allergy as those just discussed and from our own experience with food tests done both by scratch and intradermal skin tests and also by clinical trials, we believe that foods are important causes of asthma as well as other allergic conditions. Inhalants are probably more important in the United States, but not in some other parts of the world. Everything which can cause or aggravate symptoms should be considered, including such predisposing factors as infection and emotions. Skin tests for foods should not be abandoned. The scratch method for foods is fairly reliable, perhaps not as much as with inhalants. Intradermal food tests are less reliable but they should not be abandoned because they act as a check on the scratch tests and because we occasionally find a clinically important food allergen, e.g. egg or cereal, by an intradermal test, though the scratch was negative. Above all, let no one incline too much one way or the other.]

An Italian patient of Levy[300] developed severe asthma from eating fennel seed and sausage which contained fennel (closely related to the dill, carrot, celery, parsley and parsnip family). The seed is a favorite spice of Italians and is also used in medicines as an aromatic, stimulant and carminative. Asthma was reproduced by ingestion, and intradermal and passive transfer tests were strongly positive for fennel and fennel seed.

DRUGS AS CAUSES OF ASTHMA

Dragstedt[159] states that (a) drug allergy is indicated if resultant symptoms are those of allergy, e.g. urticaria, some types of dermatitis, angioneurotic edema

and asthma. Reactions characterized by jaundice, acute yellow atrophy of the liver, and optic atrophy are probably not allergic. Those with granulocytopenia, anemia, thrombocytopenia, and polyneuritis may or may not be allergic. (b) Allergy seems present if a primary or sensitizing administration of a drug appears important in the history; if drugs are long-continued or large in amounts the factor of allergy is unlikely. (c) An allergic basis is probable if relief of symptoms follows epinephrine, Benadryl or similar agents. But allergy is less likely if relief occurs after such therapy as ascorbic acid, folic acid, thiamine, or other agents whose good effects are not anti-allergic. Sherman[467] also discusses allergy to drugs, especially to tragacanth used to coat pills.

Salen and Arner[439] say aspirin allergy is the most frequent form of drug allergy, and occurs in about 8 per cent of all their asthmatic patients and twice as often in those with severe asthma. Death may occur from small doses; therefore patients and nurses should be warned. They also point out that "there are lower degrees of aspirin allergy in which the drug in normal doses only gradually—perhaps only after one to several days' medication—causes a perceptible exacerbation of the asthma, which subsides only when the drug is discontinued." Patients with aspirin-sensitivity are not more severe than the average case, despite previous reports by Van Leeuwen, Feinberg and Prickman. Prickman and Morgan[396] cite five more cases of sensitivity to aspirin, with asthma and nasal polyps, a triad frequently noted and usually associated with severe asthma and a poor prognosis (thus differing from the previous observers' opinion). In addition, there were twelve cases of drug intolerance of which four were to morphine (nausea, vomiting and in one case coma with marked asthma), and others to iodized oil, bromides, iodides and phenobarbital.

Reactions to drugs are very numerous, often with urticaria and/or dermatitis, but asthma may result as in the following case reports. Thiamine caused severe itching, inflammation, asthma and collapse, with recovery after epinephrine; this patient of Shapero and Gwinner[465] gave positive scratch and intradermal reactions with dilutions as low as 1 mg. per c.c. (controls gave positives only with dilutions of 25 and 50 mgs. per c.c.). Fineberg[184] reports two cases apparently due to nicotinic acid. In one of these substernal tightness, burning, tachycardia, cardiac irregularity and prostration occurred after the sixth intravenous injection of 150 mgs. Relief followed a little epinephrine. Skin tests with 1 per cent nicotinic acid were positive in one case, negative in the other. Barnett[51] reported four deaths, three with autopsies, after the use of "Analbis" suppositories, a bismuth compound said to be effective in upper respiratory infections and said to be non-toxic. One boy aged six, with asthma, received daily suppositories for three weeks, none for four days, then four in 48 hours for pharyngitis. On the fifth day the pharyngitis subsided, tonsils were removed (ether), and coma and death occurred thirty-six hours later. In this case and in the other two autopsies cerebral edema and fatty liver were found. These suppositories have been withdrawn from the market and are being studied.

A fifteen-year-old patient of Whittemore and DeGara[557] was given 0.5 gm. sulfadiazine for recurrent furunculosis. Within ten minutes there occurred cough, itching thighs, flushed face, and wheezing, and in five minutes symptoms of suffocation with marked hoarseness and unintelligible speech, also large wheals. This girl had received this drug about three weeks previously. Relief was obtained with Adrenalin. There was also a history of previous asthma. Scratch tests were strongly positive with sulfadiazine and much larger with sodium sulfadiazine, and also with thiazole. Passive transfer was positive with diazine and thiazole (control negative), and this phenomenon was also positive ten days, twenty-five days and seven months later—all this proving the sulfadiazine sensitivity. Tests for other sulfa drugs were negative. Frouchtman,[205] from Barcelona, had an asthmatic patient with infected tonsils. Sulfathiazole seemed to aggravate her asthma. As a test a small quantity of this drug was blown into the patient's nostrils, with resultant severe asthma, followed by collapse. Later, the ingestion of the same product (Cibazol) did not produce immediate effects but that night the patient had some dyspnea. Intradermal and passive transfer tests were positive with this drug. Penicillin rarely causes asthma but Kohn's[286] two-year-old boy received three intramuscular injections, each 300,000 units; six days later the child developed severe asthma, with relief by epinephrine. [This patient received sulfadiazine for four days before penicillin was started; perhaps the asthma here was a delayed sulfa reaction?]

A nurse with dermatitis was tested with 0.05 c.c. stock solution of streptomycin. Within two minutes a severe constitutional reaction occurred, with generalized itching, wheezing, abdominal cramps, and collapse. Fortunately, she was revived by epinephrine and Pyribenzamine. She had never had previous injections of

streptomycin but in her work was in contact with this preparation. Passive transfer test was moderately positive. After forty-eight hours the site of the original intradermal test looked like that of a positive tuberculin reaction (Rosen[426]). Sonck[480] reports asthma in a woman physician who developed her symptoms not only by inhalation of salvarsan but also by absorption through breaks in her skin. Abdominal cramps, flushing of the face and urticaria also occurred, with some relief from antihistaminic drugs.

MISCELLANEOUS ETIOLOGIC FACTORS IN ASTHMA

Jose Cortez and his associates[132] tested sixteen dogs intracutaneously with common inhalants, foods and ascaris extracts, with positive reactions for extracts of house dust, feathers, goat and cattle hairs, orris root, ragweed, pyrethrum, tobacco, cottonseed, wheat, milk and soybean. Passive transfer was positive with dust, feathers and goat hair, but failed with pyrethrum. In two of these dogs the positive reactions were so clinically significant as to give further proof that allergy is not confined to man. In an effort to correlate the bacterial content of the air with allergy Frouchtman and his co-workers[204] identified eight different strains of bacteria (Barcelona). A most unusual happening occurred in Paris. A woman developed asthma and rhinitis from inhalation of horse serum with which she filled ampules. She gave negative skin and clinical tests for horse dander. Passive transfer was strongly positive with the serum, negative for dander. She was sensitive to raw horse meat, but not to cooked horse meat nor to any other animal serum (Blamoutier[73]).

A very important letter by Mills[131] states that "control of smoke production by the policing of the multitude of city flues has been demonstrated to be ineffective and is being abandoned in favor of regulations which make harmful smoke production impossible. Such regulations prohibit the sale of highly volatile coal for use in hand-fired furnaces and enforce a change to Diesel or electric power for railroad switching purposes within metropolitan limits as the two most important points in smoke control. In view of the exceedingly significant relationship of air pollution to respiratory disease death rates in industrial cities, it is important that those interested in personal and public health insist on really effective legislation whenever the matter is under consideration in their home community." This latter is all the more significant since the recent disaster in Donora, Pennsylvania, in which those who died or were seriously ill were, for the most part, victims of bronchial asthma or heart disease. [In our next review we should have authentic information on this disaster.]

Some predisposing factors are emphasized. Zivitz[570] stresses the importance of home environment, infections, irritating vapors, and meteorologic, climatic and psychosomatic factors. Based on a study of fifty allergic patients, eighteen of these could not be properly evaluated without attention to one or more of the above factors, and he points out that such a factor may explain the variable reactions to an antigen. Clusellas[118] studied attacks of asthma in each month of the year. He concludes that the meteorologic factor must be considered along with the psychogenic, allergic and reflex angles. Humidity, temperature, wind velocity and rain were not constantly involved in attacks of asthma but a rise in barometric pressure is asthmogenic; the patient is usually better when the pressure is low. The Weather Bureau officials were consulted but they did not believe that atmospheric changes were the determining factors per se; they said the relationship of allergens in the air as affected by barometric pressure may be important. Jolicoeur[274] attempts to relate disturbances of the ovary to asthma.

Alvarinas and his co-workers[21] found that as many persons with allergy as without had intestinal parasites. In those with both allergy and parasites treatment of the parasites gave good and poor results. "Infestation with parasitic worms produces a hypersensitivity that is evidenced on skin test by an immediate wheal from intradermal injection of an extract and the finding of transferable antibodies (reagins). These facts provide the basis for the possibility that allergic manifestations such as asthma can be produced by hookworm infestation. Reports of authenticated cases were not found in the literature. Elimination of the hookworm infestation is the logical procedure in such a suspected case."[26]

Two papers question allergy as a cause of asthma. Jacquelin[270] says that only one-fifth of his cases are due to allergy; most are due to a constitutional disease, the treatment of which is the only way to get permanent results. This constitutional background is a mixture of disorders and dysfunctions of various glands and organs, the basis of which should be found in (a) heredity (neuro-arthritism and occasionally hereditary syphilis) and (b) tuberculous infection of early childhood. Hence treatment should include those usually given for allergy plus all

sorts of treatment of the exudative diatheses (cholagogues, sulphur, phosphoric acid, magnesium, et cetera, as well as measures for the supposed tuberculosis). Another paper by Lewi[301] states that hay fever is not due primarily to pollens [Blackley should rise from his grave] but is the result of abnormal conditions of the mucosa of the upper air passages. The author also believes that asthma is not due to allergens but to dysfunction of the sympathetic nervous system, and his treatment brings on hyperemia by the high frequency current applied along the spinal cord. Lewi claims complete and permanent relief in over 60 per cent of those treated (1,600 cases of asthma and related conditions), with great improvement in an additional 30 per cent.

[These last two papers should not go unchallenged. They are a throwback to our knowledge before clinical allergy became established. We used to talk glibly about this or that diathesis and we still know little about diatheses. Anyone who has been interested in asthma and hay fever knows that diatheses, except for the hereditary factor, mean little or nothing in these conditions. We do know that pollen causes asthma and hay fever and dust and other allergens lead to asthma and rhinitis in allergic persons, the local condition of the nasal mucosa being of little importance. The "marvelous results" obtained in the second paper cannot be accepted nor is the thesis of the first paper compatible with our present knowledge.]

The psychogenic factors in asthma will be discussed in the section on treatment (q.v.).

IMMUNOLOGY AND PATHOGENESIS

Easily the most outstanding paper of the year is by Warren and Dixon.[552] The location of the antigen-antibody reaction has been one of the most disputed aspects of anaphylactic shock. By using an antigen labeled with radioactive iodine and employing tracer techniques they have been able to recover sufficient antigen concentrations during the shock. The antigen was found in edematous bronchial fibrous tissue of the guinea pig. They then studied the stages in the development as well as the final picture of bronchial obstruction during shock and also bronchial obstruction produced by drugs acting on smooth muscle. Significant amounts of labeled antigen were found only in the liver and lung during anaphylactic shock. Since the amount of antigen taken up and its distribution in the liver were the same in sensitized and non-sensitized animals the liver evidently is not important as regards sensitivity. The startling finding was the fact that the affinity for antigen by sensitized lungs in fatal shock was about twice that seen in controls and therefore presumably a function of the sensitivity. The increased amount of antigen taken up by the sensitized lungs was found in edematous bronchial fibrous tissue. They were unable to confirm the generally accepted theory that bronchial obstruction of anaphylactic shock results solely from contraction of bronchial smooth muscle. Only in the early stages of shock (within two minutes after the onset of respiratory distress) was there convincing morphologic evidence of smooth muscle contraction, and even in these early stages there was already some edema. In the terminal stages of shock the smooth muscle did not appear contracted or otherwise abnormal. The bronchial edema which began to form during the early stages of shock became massive in the terminal stages and at that time appeared to be the most important factor in the production of bronchial obstruction. Since this edematous zone was the site of antigen localization, it seemed possible to the authors that the antigen-antibody reaction was related to the formation of edema.

[One cannot praise this work too highly. By the tracer technique with radioactive iodine they have given us authentic information. We have always believed that edema and excessive mucus formation were the important causes of the incomplete obstruction with resultant wheezing which is so characteristic of bronchial asthma. We have never thought that bronchospasm was important in asthma and there has been little or no verification of the theory of bronchospasm by bronchoscopists. Yet some writers persist in using the terms "bronchospasm" and "bronchial asthma" interchangeably. They are not the same, in our opinion, at least. When, at autopsy, one sees the extensive mechanical obstruction by the dried-out sputum he cannot but be impressed by the major role of edema and mucus. Hypertrophy of bronchial muscles does occur but only in chronic asthma of long standing. Heart failure is a rare cause of death in bronchial asthma. This paper goes a long way to substantiate the "edema" theory of asthma.]

To Miller[346] bronchial asthma is due to the pharmacologic action of histamine on the bronchi. This drug (a) dilates terminal arterioles and venules, (b) increases capillary permeability, causing swelling of the bronchial mucosa, (c) stimulates smooth muscle, causing bronchospasm, (d) stimulates exocrine glands, causing an

outpouring of mucus from bronchial glands, (e) stimulates sensory nerve endings, causing itching and cough, and (f) calls forth eosinophiles. The three factors which lead to narrowing of the bronchi (spasm, mucus and edema) in turn cause emphysema, hypoxemia and hypoxia. Anything which can cause the above phenomenon can cause wheezing and dyspnea, e.g. a foreign body or pressure from without by a tumor or aneurism—in other words, bronchial asthma is not necessarily an allergic phenomenon. [We strenuously object to this latter statement. We believe that true bronchial asthma is always allergic. It is true that in perhaps 20 to 25 per cent of the cases we fail to find the causative factors. Nevertheless, if we search and continue to search we will, in many patients, ultimately find the cause, with benefit to the patient. We believe that non-allergic conditions, e.g. foreign bodies and tumors, should not be listed as causes of bronchial asthma even if they do cause "asthmatoid" symptoms. They constitute the diseases which we will shortly discuss in the section on differential diagnosis. Furthermore, we by no means agree with Miller's wholehearted acceptance of the histamine theory as the cause of the symptoms of bronchial asthma and other allergic diseases.]

Abramson,[3] among others, stoutly denies the histaminic theory of allergy, and quotes seventeen experimental findings which are incompatible with that theory, among them the fact that antihistamine drugs can control bronchial obstruction due to histamine but not when due to allergens, whereas epinephrine readily controls both.

Bronfenbrenner[83] believes in the "unitarian" hypothesis of hypersensitivity and immunity: the phenomena of specific heightened resistance and heightened sensitivity are different expressions of a single biologic process. Only one antibody is produced and this can be recognized by a variety of procedures, some direct, others indirect. Burnet,[97] also an immunologist, believes that genetics and immunology will soon be linked in a productive attack on some of the most fundamental problems of biology. From such an attack may come knowledge of high significance for human medicine, not least in the field of allergy. Cooke[126] points out that in spontaneous (hereditary) asthma and rhinitis the vasodilation, with edema in sensitized tissues, and the increased secretion of mucus all occur promptly on exposure to an allergen, e.g. a cat. H. Miller[344] has diagrammatic sketches in his article on the immunologic basis of clinical allergy. He also has a nice table differentiating the characteristics of normal antibodies and reagins.

PHYSIOLOGY OF RESPIRATION AS RELATED TO ASTHMA

An editorial in the ANNALS OF ALLERGY[170] emphasizes the importance of the physiology of the lungs in asthma. It quotes a recent paper by Mack, Grossman and Katz[325] which shows that pulmonary congestion may cause dyspnea. Mechanically, changes in the distensibility of the lungs are important. When pulmonary vessels become engorged they are more rigid and act like a hose turgid with water under pressure. It is readily accepted that this engorgement contributes to the increased respiratory effort observed in congestive heart failure. But this diminished distensibility may also diminish vital capacity and even cause intrapleural exudation. By injecting blood into the pulmonary circulation of dogs the distensibility of the lungs is proportionately decreased. When almost all the injected blood was siphoned off the distensibility curve was restored. This demonstrated clearly that the effect was due to intravascular blood which could be siphoned off and not to an intra-alveolar transudate similar to that found in pulmonary edema. In the living animal two or three of the pulmonary veins were clamped at the entrance to the left atrium. This acted much like a severe mitral stenosis with pulmonary congestion. The volume-pressure curves obtained then showed decreased distensibility of the lungs.

Brown has an excellent review of the physiology of respiration especially as it affects bronchial asthma.[86] He concludes that "respiration is a complex biological mechanism, stimulated, depressed and affected by many varied and diverse factors, no one of which operates alone." He agrees with Gray that "while a number of factors exert independent effects upon respiratory ventilation, they are also mutually interdependent, so that a change in any one factor usually brings about changes in one or more of the other factors, the actual ventilation being defined as the algebraic sum of the partial effects of the separate agents. Since these lend themselves to mathematical description, it is possible to reduce them to working formulae."

Hickam and Cargill[257] took advantage of the newly popularized technique of intracardiac catheterization with penetration into the pulmonary artery. With eight normal individuals as controls, they tested many patients with cardiovascular disease

and emphysema; in the latter group the resting pulmonary pressure, with one exception, was higher than in the normal. On exercise, pressures in the pulmonary arteries increased still more beyond the normal range. This was expected because of the narrowing of pulmonary vascular channels in emphysema.

Riley and his co-workers[417] also catheterized the pulmonary arteries of three normal persons and eight patients with various types of chronic pulmonary diseases including bronchiectasis and emphysema. In two of the three normals a fall in mean pulmonary artery pressure occurred during exercise (a slight rise in the third). On exercise all three showed a marked drop in pulmonary vascular resistance and a minimum increase in work of the right ventricle. On the other hand, three of the eight patients at rest showed an elevation of pulmonary artery pressure and all developed increased mean pressure during exercise. The pulmonary vascular pressure remained stationary or was increased at the same time, and the work of the right ventricle was always greater in these patients than in normal persons at the same work level. In patients with chronic heart disease the rise in pulmonary arterial pressure with exercise is due to decrease of arterial oxyhemoglobin saturation and increased pulmonary resistance resulting from lung tissue destruction, interstitial pulmonary fibrosis, or vascular sclerosis.

Gray and Green[228] have a fine article on the voluntary ventilation capacity in normal individuals. They have standardized the procedure so that it is a very useful clinical test of the functional capacity of the respiratory tract. They point out that the "ventilatory capacity may be measured as the maximum possible respiratory minute-volume. Ventilatory capacity in this sense depends upon two primary factors, the functioning lung volume (vital capacity) and the dynamic flow of air through the respiratory passages. These two factors may be affected *independently;* there *may* be reduction in the vital capacity with little change in resistance to the flow of air, as in pneumothorax, or there may be increased resistance to the flow of air with little change in vital capacity, as in bronchial asthma. As a result the vital capacity alone is *not* a measure of ventilation capacity. Unfortunately, it has been commonly interpreted as a measure of ventilation capacity but this interpretation is clearly fallacious."

Using a modification of a standard Benedict-Roth spirometer the individual is instructed: "This is a test to determine how much air you can breathe in and out of your lungs in twenty seconds when you breathe just as hard as you possibly can. In order to move the most air, you mustn't concentrate on breathing only fast, or only deep, but instead you must compromise between the two in such a way as to maintain the most rapid flow of air in and out of your lungs." In eighty-nine aviation students the reliability coefficient of the test was 0.90. The mean ventilation capacity was 168 liters per minute, with a standard deviation of twenty-two liters per minute. The ventilation capacity was found to be correlated with surface area, but not with age, height or weight. [This method is obviously much more accurate than is the simple, vital capacity technique which most of us have used in the past. An asthmatic patient may be able to take one deep inspiration and expiration, and his vital capacity as judged from this one respiratory act may well be 50 to 75 per cent of normal. But this same patient's ventilatory capacity will have a much lower percentage than normal, perhaps only 5 to 10 per cent, because he simply cannot breathe deeply and rapidly over a period of twenty seconds as required by the new test. The test therefore fits in with clinical experience, e.g. dyspnea on such exertion as climbing one flight of stairs, much better than does the vital capacity test. The test is simple and very much worth while.]

Tuft, Blumstein and Heck[517] also review the physiology of the lung with particular attention to external and internal respirations and the circulatory status. They agree with the previous authors. Their patients are asked to breathe rapidly and forcefully for thirty seconds, and their "maximum breathing capacity" (B.R.) is similar to the ventilatory capacity previously described. The B.R. corresponded to the clinical degree of asthma in all twenty-two cases, all of whom had more or less emphysema. They also estimated the B.R. before and after giving 0.50 c.c. epinephrine. In those whose B.R. remained low even after epinephrine there was also a clinical low tolerance for exertion—this invariably due to pulmonary fibrosis or emphysema, either resulting from or associated with the asthma. The absolute functional pulmonary impairment can only be determined after elimination of as much bronchoconstriction as possible by such a bronchodilator as epinephrine. The degree of disability invariably parallels the results of this dynamic type of spirometry and will not necessarily bear a constant relationship to the changes in the size or shape of the chest.

Jiménez-Díaz and his co-workers[271] describe their experimental arrangements and show that differences in the filling with blood of the smaller circle are accompanied by parallel differences in the air volume and rigidity of the lung. As an increase

in the vascular filling of the lung is produced, the breathing lung dilates, producing a true emphysema and at the same time a rigidity which makes expiration difficult. Thus, on increasing resistance in the pulmonary veins, the same phenomena are noted as in experimental asthmatic shock. The authors believe that both bronchial and cardiac asthma are sequelae of acute ingurgitation of the smaller circle. Drugs which cut short asthmatic crisis act by diminishing the volume of pulmonary blood.

Colldahl[125] states that in most severe attacks of asthma the ventilation of the lungs as well as the intake of oxygen is much lower than between attacks. When the attack is over the intake of oxygen is considerably raised. In mild asthma the pulmonary ventilation and oxygen intake are much higher than normal. [This does not apply to forced rapid breathing tests, as previously mentioned.] The intake of oxygen during such an attack may be increased at least 100 per cent. The systolic and diastolic blood pressures are usually considerably increased during severe spells, along with a fall in body temperature. There is often a moderate rise in temperature in mild but persistent asthma.

In 100 patients with asthma, Hamburger[236] measured the "average expiratory rate" (A.E.R.), i.e., the maximal quantity of air which can be expired in one second. He found that in 85 per cent of the cases, with no apparent dyspnea, the A.E.R. was 20 to 50 per cent lower than normal. In 11 per cent, with permanent dyspnea between attacks, the A.E.R. was more than 50 per cent below normal. This proves that in many asthmatic patients who appear to be symptom-free between spells there is a permanent subclinical respiratory deficiency. [Of course, one could guess this by questioning asthmatic patients closely as to how much exertion they actually can tolerate when they say they are free from asthma. Probably the only ones who are 100 per cent symptom-free between attacks are those more fortunate individuals who are allergic to substances which they only meet at long intervals, e.g. a certain pollen or animal or a food eaten only occasionally, e.g. a particular nut. The A.E.R. is, however, useful, although the ventilatory capacity test or the B.R. test, just described, are much more accurate.]

PATHOLOGY OF ASTHMA

Deaths continue to occur even though the incidence is very small as compared with the number of attacks. The findings at the autopsies recently reported are much the same as in previous years. A thirty-four-year-old asthmatic patient of Wakefield and Hirsch[540] entered the hospital for the fourth time but she failed to respond to the usual measures. Coma set in with death on the third hospital day. At autopsy the usual inspissated mucinous obstruction of the bronchioles was found, along with emphysema. The left lower lobe also showed atelectasis, hyperemia and bronchopneumonia; focal atelectasis in the lower right lobe and focal fibrinous pleuritis at the right apex. Death apparently came from suffocation. [Bronchoscopic aspiration was not done—it might have prolonged the patient's life; we have undoubtedly saved several lives by enlisting the services of a bronchoscopist when the usual therapy proved unsuccessful. We strongly recommend bronchoscopic aspiration and without too much delay.]

A three-year-old asthmatic child of Tichenos and Lafsky[510] died fifteen hours after admission to the hospital. Again death was due to generalized bronchial obstruction from excessive mucus plus pulmonary emphysema. In addition, right heart failure was diagnosed, and a throat culture was positive for hemolytic staphylococcus aureus; a culture of the lungs and bronchi revealed Gram-positive diplococci resembling pneumococci. The whole picture was that of overwhelming infection in an asthmatic child. [In reviewing this case Glaser (and we agree) said that in such an emergency as this more 1:1000 epinephrine should have been given, along with aminophyllin by vein, dextrose, sulfadiazine, penicillin and oxygen. In such a case one should push large doses of penicillin without waiting for culture report.]

In Andre's case,[22] a sixteen-year-old girl died suddenly in the third attack of asthma which had occurred in the space of twelve days. The most characteristic sign was Kussmaul's pulse: weakening or disappearance of the pulse during inspiration. The mechanism of this paradoxical pulse is discussed. A sixty-four-year-old male asthmatic patient died during an attack fifteen months after the onset of asthma. Alexander, Wilson and associates[17] could find no personal or family history of allergy nor any eosinophilia nor Curschmann's spirals. Nevertheless, at autopsy there were the usual findings of fatal asthma: mucous plugs in all the secondary and terminal bronchi; generalized emphysema, hyalinization of basement membranes; hypertrophy of the muscular coats and infiltration with eosino-

philes. In addition, calcified nodules and lymph nodes were noted, along with moderate dilatation and hypertrophy of the right ventricle.

From France, where morphine is rarely used in the treatment of asthma, Villanova[537] says death from asthma seems to be increasing in frequency. Death, he believes, is due either to (a) a sudden unexplained cause, (b) anaphylactic shock, (c) heart failure or (d) asphyxia due to bronchial obstruction. He adds three more fatalities, all adults, all of whom had received great quantities of varying medications. He especially blames the sympathomimetic drugs (frequent factors), morphine (occasionally), and novocaine (some cases). He advises venesection, intravenous aminophyllin, with or without novocaine, phenobarbital subcutaneously, and injections of pilocarpine. [Sclafer, in commenting, also believes that an excess of epinephrine is a frequent cause of death. Less than 10 per cent of French pediatricians dare to use this drug in asthmatic children.]

Jiménez-Díaz and Lopez-Garcia[273] also report a fatal case of asthma. "Bronchial spasm" is a poor term because at post-mortem there is no basis for this diagnosis. Status asthmaticus, as already mentioned above, is due to obstruction of the whole bronchial tree from secretion plus hypertension of the lesser circulation which in turn causes rigidity of the lung which in turn causes difficulty in expulsion of secretions from the lungs; this in turn thickens the secretion, with an increase in obstruction.

In a fifty-one-year-old man who had asthma for about seven years the usual measures plus bronchoscopic aspirations (no morphine) failed. Melich and his associates[337] report that autopsy led to the final diagnosis of intrinsic bronchial asthma, bronchopneumonia and mild cor pulmonale. Mucous plugs were very numerous, with generalized emphysema. The right ventricle appeared slightly enlarged. In Galup's case[212] death occurred after only eight years of asthma in a man who had asthma, emphysema, chronic bronchitis, nasopharyngitis and recurrent acute pneumonitis. A unique feature in this case was the fact that the patient's diaphragm was normal in 1942, flattened bilaterally in 1943, and paradoxical in 1945, moving upward with inspiration. The cause of the phrenic paralysis was discussed but there was no definite conclusion.

In Gay's article on the Pathology of Asthma[216] he reviews the literature and adds twenty-four cases from Johns Hopkins Hospital with a clinical diagnosis of bronchial asthma either as a primary or secondary cause of death. [These cases were also discussed in his book mentioned in our last review.[521] Deaths can often be prevented by the prompt use of penicillin in any acute case in which infection is present or suspected; three of the twenty-four deaths were in children, in whom infection is frequently severe and sudden.]

In Peterson's case[383] death followed mediastinal and subcutaneous emphysema which occurred during an attack of asthma. Up to 1945, twenty-six cases of spontaneous emphysema of this type had been reported in asthma, with no fatalities. In this case death occurred in a twenty-year-old primipara, gravid four months, who entered the hospital with severe dyspnea and anxiety. She had asthma for eight years but none for the two years preceding this pregnancy. Asthma returned in the second month of pregnancy and became progressively worse. Extreme restlessness was not controlled by oxygen, helium, aminophyllin, barbiturates, ether in oil, and even demerol and a little morphine. On the second day swelling of the neck was noted, with spread to the face and anterior thorax and increased respiratory distress and death thirty-six hours after admission. At autopsy plugging of practically every small visible bronchus was found. The mediastinal and subcutaneous tissues of the neck, face and thorax revealed marked emphysema, but no pleural air was found when the lungs were opened under water. The outstanding findings were the large amounts of mucus with plugging, widening and hyalinization of basement membranes and numerous eosinophiles. The muscles of many large bronchi were hypertrophied but that of many smaller bronchi were thinned with small areas of saccular bronchiectasis. The author states that since all the other cases recovered the cause of death in this case was undoubtedly bronchial asthma; the use of morphine was a serious error. The associated subcutaneous emphysema was, in all likelihood, not responsible for the exitus. Even the use of demerol in asthma is of doubtful value. [We agree, and recently, in addition to our absolute avoidance of morphine in bronchial asthma, we are using less and less demerol; the less sedation the better the results.]

A twenty-year-old sailor, known to be egg-sensitive, died twenty-six minutes after an injection of typhus vaccine. Autopsy revealed only intense pulmonary congestion, according to Walker.[547]

Two other papers on pathology should be mentioned. Bohrod, whose lectures and slides on asthma and related conditions are superb—they should be put out

in book form—classifies the histologic reactions in allergic diseases.[76] Anatomic differences in these lesions divide them into a relatively small number of groups each of which also has clinical and immunologic similarities. No lesion is pathognomonic of allergy but all are highly characteristic and their presence suggests allergy as a cause. But many of the lesions can be both allergic and non-allergic in origin. Bohrod classifies the diseases of allergic and possible allergic origin, according to their histologic lesions (necrotizing, cell selective, anaphylactoid, and granulomatous). Asthma, anaphylaxis, serum sickness, atopic dermatitis, caseous tuberculous pneumonia, and rheumatoid pneumonia belong in the anaphylactoid group.

According to Soulas[482] deficiency in the defense power of the bronchus is due to (a) changes in the bronchial wall with edema with possible resultant erosive inflammation or ulceration and sometimes associated with an involvement far below the surface, e.g. necrosis, stenosis or new growth; whether superficial or deep, the parietal lesion lessens the secretion of mucus. (b) There is also deficient expulsion of bronchial secretion, due not only to the deficient vector represented by the cilia and the mucus, but also to (c) lessened motility of the wall. As a result, obstruction, stagnation and retention may occur. Bronchoscopic treatment should try to relieve obstruction by clearing the bronchi and by restoring their secretory, excretory and motor power.

SYMPTOMATOLOGY OF ASTHMA

Since the symptoms of asthma have been adequately described, even many years ago, most papers in this field deal with classifications, laboratory aids, and complications. Many are concerned with asthma in children, with a few about the elderly.

Simon[471] discusses the definition and language of allergy, its origin, development and significance, and allergenic interrelationships. Is histamine actually the substance, or the only substance, involved in allergic reactions? He discusses various aspects of the pathogenesis of asthma, with no definite answer.

To Rackemann[402,405,406] asthma is both a symptom and a disease. The typical patient can wheeze from a great variety of causes of which allergy is only one. Patients who develop asthma before thirty are "extrinsic" in type, although there may be complications, e.g. infection or "depletion." If asthma begins after forty they are "intrinsic" and associated with bacterial allergy, "depletion," psychosomatic factors, and occasionally with tumor or foreign bodies. [As pointed out in previous reviews, this classification by age into "intrinsic" and "extrinsic" seems to us to be a block in the road toward solution of the problem. When one says "intrinsic" he is apt to give up, to tell the patient to go to Arizona or California or Florida or into the mountains or down to the coast. We feel that there is little distinction between the two groups—both have about equal eosinophilia in the blood and sputa, and both have similar wheezing, dyspnea and cough. In the "intrinsic" group the patients are older and there is naturally a greater tendency to cardiovascular complications, to chronicity, to loss of morale and weight, and because the skin of older people is less sensitive, to more negative skin tests. But we have found positive skin tests in many elderly asthmatic patients and have occasionally had negative skin tests in children with asthma. Very recently, we relieved the symptoms in two men by finding positive test for karaya gum, used to hold up their upper dentures. Many allergists never test for karaya gum; they would have called these two patients intrinsic because they were elderly and because other skin tests were practically negative. And experienced clinicians like Rowe have shown, as previously stated, that many older asthmatic patients are allergic to foods in spite of negative food-skin tests.]

To Baagbe[42] "allergy" means "a changed sensitivity due to the formation of antibodies." Thus his "allergy" includes both anaphylaxis and immunity; the definition is on a serologic basis. He considers three factors: (a) a main disposition to become allergic, (b) an accessory disposition toward a particular allergic condition, and (c) in rarer cases an inherited allergy to a particular allergen, e.g. egg.

Farrerons-Co[176] reviews other classifications of asthma, then submits his own:

(a) Endogenous (mild, moderate, severe)
(b) Infectious (focal, bronchial)
(c) Parallergic (due to pure parallergens or bacterial parallergens)
(d) Allergic (foods, inhalants, mixed foods and inhalants)
(e) Combined (allergens and bacteria) (bronchitis)

Alemany-Vall[524] discusses lesser allergies, either manifest or hidden, e.g. sinusitis, tracheobronchitis or mild asthma, as well as various types of allergy in other parts of the body. Forman[190] mentions certain clinical aspects of asthma, and Baagbe[43] rightly emphasizes the importance of pre-asthmatic bronchitis, with severe attacks of cough without wheezing, or winter attacks of bronchitis over many years in children, often associated with fever and frequent "colds"—all these symptoms finally, though not necessarily, culminating in a real attack of asthma.

Philps[384] describes a thirty-year-old patient who has asthma, eczema and cataracts. The latter two are associated fairly frequently, but the additional presence of asthma is very rare. Since the lens is ectodermal in origin it is not surprising that it should develop defects when the skin and epithelial lining of the air passages are also affected. Her asthma was so severe that the cataract operation had to be performed with the patient sitting up. Peralta and Valle[380] emphasize history-taking in bronchial asthma, and Bruce-Peterson[92] was surprised to learn that in the United States 50 per cent of patients with hay fever develop asthma unless properly treated. In Britain there is no ragweed and therefore the incidence of pollen asthma must be much lower.

In a two-year-old patient of A. Brown,[84] attacks of asthma followed periods of intense craving for and indulgence in carbohydrates. With each spell of wheezing and dypsnea the stools became loose, frothy and offensive; then the craving for sweets disappeared, the stools returned to normal, and the attacks subsided. A high carbohydrate diet brought on symptoms within twenty-four hours. Irritability was a striking symptom, but all symptoms again subsided when a low carbohydrate diet was substituted for the high. [Despite the diagnosis of asthma in this case there appear to be no diagnostic features of allergy, e.g. family or personal history, positive skin tests, or eosinophilia. We wonder if hypoglycemia of some type might be a factor perhaps due to an adenoma of the pancreas; for occasionally, in diseases involving the middle layer of the cortex of the adrenal glands, a heavy carbohydrate meal is followed by prolonged periods of hypoglycemia. Blood sugar and other tests should be carried out.]

Another interesting case occurred in a seventeen-year-old asthmatic boy. Digestive symptoms were also marked for about a month, and when x-rays revealed a huge stomach 0.03 gram of ephedrine was given daily, later three days a week, for a total dose of twelve grams over a period of sixteen months. The symptoms were alleviated and the stomach shrunk to normal size (Hillemand and associates[260]). This case is analogous to that of Zeller's patient, a sufferer from asthma and hay fever, whose asthma was relieved by an intravenous injection of 0.50 gm. aminophyllin. In addition, her marked abdominal distention (intestinal obstruction?) also disappeared. Several other episodes of distention in Zeller's patient were also promptly relieved by aminophyllin.[566]

Conn and Wolf[124] found that those with allergic respiratory tract disease, chiefly asthma, had increased palmar sweating as determined by the Silverman technique, and as compared to other patients with psychoneurosis and others with syphilis. Race, sex, and age were without influence. The increased perspiration is thought due to disturbed water balance and to cholinergic stimulation. They conclude that allergic respiratory disease in man is dependent on an inherent behavior pattern of the autonomic nervous system in addition to hypersensitivity.

Feinberg[177] discusses allergic problems of the railway surgeon. These consist of (a) allergy in employes, not related to the unemployment, (b) allergy due to conditions of employment, and (c) allergy relating to passengers and the public. Railroads are advised to (a) lessen the amount of smoke, (b) have available dust-proof casings for mattresses and pillows of allergic passengers, and modifications of diets which could be substituted for such foods as egg, wheat and milk, and (c) have ready information for passengers concerning pollen and fungus counts in various parts of the country.

ASTHMA IN CHILDREN, WITH REMARKS ON TREATMENT

This subject has provoked many articles. Dees and Lowenbach[149] found cerebral dysrhythmia, chiefly occipital, in fifty-two of eighty-five allergic children, with no relation to behavior problems in these children nor to convulsive history or findings. The incidence was higher among children with persistent allergic symptoms. The percentage of this dysrhythmia was about 50 per cent nonallergic children, even in those with convulsive disorders of behavior problems.

Nance[356] reports seven cases of asthma in the newborn—it is probably the most frequent cause of wheezing in infants. One should not accept the diagnosis of thymus enlargement as the cause of noisy respiration in the newborn on the basis of roentgen observations alone. At this age the cause is almost always dietary

and detection and removal of the offending food is simple. Hill[258] says that atelectasis can occur in the newborn, usually due to aspiration of amniotic fluid. Bronchoscopy should be done as soon as possible. And Cohen and Abram[123] utilized the grid technique described by Wetzel to study growth patterns. From 503 observations in 150 allergic children seen in private practice as compared with 622 observations on 102 nonallergic controls, they conclude that (a) allergy occurs more frequently in children (especially boys) who, by inheritance, are constitutionally slender; (b) allergy is a common cause of growth failure; (c) control of active allergy is accompanied by a corresponding growth repair if an adequate diet is available.

Black[69] states that the incidence of childhood infections in asthmatic children is no greater than in those who are non-asthmatic. He has never seen pulmonary tuberculosis in an asthmatic child under the age of ten, and death from asthma in children is very rare. Julia Baker,[45] in a seven-year study, believes that altitude is important in initiation and severity of allergic reactions. Symptoms are unduly common and severe at the high altitude of Mexico City (7,325 feet) and appear frequently in children not noticeably affected at lower altitudes. In 1000 children 509 were allergic, and sixty-two were sicker in Mexico City than when they lived at lower altitudes. Symptoms frequently followed ingestion of such foods as egg, milk, orange, chocolate and wheat. Infection was not a factor as shown by studies of blood and stools. Mexican children and those from the United States and other countries were about equally affected.

Glaser,[223] in his annual review of pediatric allergy, has an excellent summary of psychosomatic aspects. The child's symptoms should not be discussed in front of the child but it should be told that it is progressing nicely and encouraged to play as much as possible. However, the best that can be hoped for from the psychologic approach is amelioration, rarely a cure, because no psychological treatment can change the underlying allergic constitution. Once we are able to relieve, at will, the allergic manifestations, the psychological problems associated will, in most instances, solve themselves." Glaser stresses the seriousness of asthma in infants and children. Prompt therapy is necessary and should include epinephrine, aminophyllin, oxygen, bronchoscopy, penicillin, and/or sulfa drugs.

There are several more general papers. Bowen[78] has a fine article on asthmatic children. He stresses a good history. In one group 90 per cent had a positive hereditary factor, and when inheritance was bilateral 90 per cent of the children developed allergic symptoms before ten; with unilateral inheritance about 30 per cent. Those who are milk-sensitive are given dicalcium phosphate and Mullsoy, Allerteen or goat's milk. He believes, with Ratner, that those who are allergic to corn can safely eat foods with pure corn syrup, Dextrimaltose and crystalline sugars. Food skin tests are less than 40 per cent reliable. Some foods can be tolerated once a week but not three or four days in succession. Food dislikes are not necessarily associated with allergy; a child may like an allergenic food. The fewer the nose drops the better—when necessary he prefers Neosynephrine ¼ to ½ per cent. He has an excellent outline for treatment, with remarks on the use of epinephrine, study of the home, hobbies (e.g. glue exposures), and complete avoidance of morphine. And, like Glaser, his allergic children are encouraged to play as much as possible.

Logan[313] uses scratch tests in children up to five, with a few selected intradermals. Older children receive intradermal tests except for foods—he uses only thirty-six antigens for routine testing. He points out that asthma in children is often incorrectly diagnosed; the child may merely have excessive saliva or mucus, or an acute laryngotracheobronchitis, or even "sighing dyspnea," among other conditions. [We do complete scratch testing (about 200 or more) in all allergic patients, from infancy to old age, and follow by intradermal tests when sufficient information is not obtained. In infants the chest and abdomen are usually used, in older children and adults the arms. One is often surprised to find a positive reactor which fits in clinically even though a painstaking history was negative for this allergen—witness those who are allergic to cottonseed or karaya gum.]

In 265 children with asthma, Buffum[96] found eighty-five (32 per cent) with onset before the age of two. Of these, twenty-nine (34 per cent) were severe as compared with thirty-seven (20 per cent) with onset after two. Superimposed infections frequently increase and prolong the bronchial reaction, with excellent results from sulfadiazine and/or penicillin. Skin tests in children were invaluable, and 61 per cent of his children were completely or almost completely relieved of their symptoms, with 87 per cent helped (three-year followup).

Archibald[40] stresses the long-range point of view in allergic children. He uses scratch tests on the back, with positive reactions in about 75 per cent of cases of re-

spiratory allergy. He likes the Rowe-type diets and emphasizes avoidance of house dust. McGee[321] studied 150 healthy babies to recognize allergic tendencies at their onset. Foods were given one at a time and the babies seen once a month. Persistent food dislikes did not parallel food allergies. Foods which caused symptoms during the first year of life, in order of frequency, were orange, boiled cow's milk, spinach, ascorbic acid, mixed cereals, prunes, tomato, codliver oil, carrot, oat, and wheat. McGee[322] also points out that "croupy" infants frequently develop bronchial asthma or bronchitis. If tonsils and adenoids are removed outside of the pollen season hay fever and asthma occur less frequently. Epinephrine is excellent for respiratory symptoms, especially in unilateral atelectasis. [We in the United States frequently use small doses of epinephrine in asthmatic children. Those in France, Cuba, and perhaps other countries seem afraid of this drug. Could they be injecting epinephrine stronger than our standard 1:1000 dilution?] McGee says that when skin tests are necessary for children under seven or eight the passive transfer method is best. It prevents needle-phobia [what about ordinary immunizations?] and does not destroy the child's morale. In addition, an adequate survey is possible in any place since the defibrinated sterile plasma, and the summary of the history and physical findings can be sent by mail to the allergist. [This revolutionary technique smacks of "mail-order" medicine. We certainly strongly oppose such practice as there is no substitute for a personal history and examination of patients. Furthermore, skin tests can easily be made in children of all ages, especially if the scratch technique is used to begin with. All one needs is a little patience and a kindly and playful attitude with these children; the removal of a parent may help.]

In Honolulu, Myers[351] says molds are more important than pollen. He also discusses differential diagnosis of asthma in children. He uses intradermal tests but says he "guards" against possible danger by having epinephrine and a tourniquet on hand, and just omits testing for those allergens which give a positive history. He only makes six to ten tests at a sitting. If all skin tests are negative he uses Hapamine. O'Keefe[364] says foods are the most common cause of asthma in children under three; from three to seven animal emanations are most important, and after seven, pollens lead, with bacteria later. He uses scratch tests, supplemented by intradermal tests if necessary.

Pounders[393] says that treatment should be as simple as possible so that it can be carried out. He quotes Shakespeare: "If to do were as easy as to know what were good to do, chapels had been churches, and poor men's cottages princes' palaces." General papers on allergy in children also come from Bentolila,[58] Pennington,[377] Slesinger,[474] and Smyth, Bowen, et al.[479] Rucks[433] emphasizes the difficulty in differentiating the infectious and allergic types of asthmatic bronchitis in children, especially if the allergic condition is associated with some other type of chest disease.

Prophylaxis in children is discussed by Shulman,[468] especially as regards new foods and the environment. Roberts[420] wrote "Protecting Your Child from Allergy" in *Hygiea* magazine. The article is very good, although Glaser rightly says "Roberts, a layman, quotes various pediatric allergists as having made the statement in a round table discussion at the ninth annual meeting of the American Academy of Pediatrics to the effect that 'Fifty per cent of the allergic cases in the nation may be avoided by stressing certain preventive measures which parents can take.'" Glaser adds "it is unfortunate that such a dogmatic statement should have been made in a journal intended to inform laymen on the progress of medicine, since there is no scientific evidence whatsoever of the truth of this statement. There is at present only presumptive evidence that allergy may be prevented by use of certain measures which are very reasonable and should be carried out because of this and the equally important fact that they can do no harm."

From Sweden, Salen[438] discusses the diagnosis, treatment and prognosis of asthma in children. Of eighty-five children with severe asthma, recovery, complete or almost complete, occurred in seventy-four (94 per cent). His therapy is similar to ours except that his patients also inhale eucalyptus tar. The prognosis is good if treatment is begun before the onset of such complications as emphysema or purulent bronchitis.

Horesh[263] has two interesting case reports. An eight-year-old girl developed convulsions four hours after the eighth injection of ragweed extract. It was felt that the convulsions had nothing to do with this injection but when an increased ragweed dosage was given a week later even more severe convulsions occurred in four hours. Hyposensitization was stopped with no further convulsions in the following five-year period. The author agrees that the second injection should not have been given. [Bizarre reactions occasionally occur during hyposensitization. We have a ragweed-hay-fever-asthma patient in whom small dosages twice brought

on unexpected vaginal bleeding. Much smaller dosages have been given without further trouble.] Horesh's second case is "sighing dyspnea" in a thirteen-year-old girl whose brother has asthma. The mother was certain the girl was also developing asthma, and the girl had an almost uncontrollable desire to fill her lungs with air at five or ten minute intervals, taking deep breaths and complaining that she had difficulty in taking them.

In Bowman's series,[79] 90 per cent of twenty-five cases of purely infectious sinusitis, without allergy, were cured by x-ray therapy; this treatment was followed by clearance of sinuses, disappearance of thickened membranes, and lessening of lymphoid hyperplasia in the nasopharynx. In many of these cases the child's cough is the predominant symptom, and the sinusitis which causes the cough is overlooked. The ethmoid and maxillary sinuses are most commonly infected in children. In addition to x-ray treatment it may also be necessary to use nasal vasoconstrictors judiciously, to eliminate allergic factors, if present, to remove infected tonsils and adenoids, and to correct any nasal abnormalities which block drainage.

DIAGNOSIS OF BRONCHIAL ASTHMA

In a scientific exhibit in June, 1947 (American Medical Association), and later published,[522] L. Unger, H. Levy, A. H. Unger and Eisele outline the diagnosis, complications, differential diagnosis, causes, and treatment of bronchial asthma. Included are four murals depicting "Asthma Through the Ages," as well as x-ray films, photographs of twenty men whose contributions have been outstanding in this field, and pathological studies.

Samter[440] found Charcot-Leyden crystals in the blood of patients with high absolute eosinophilia; the crystals originate in individual eosinophiles, but crystals develop in only a minority of eosinophiles. Dutton[166] studied forty-three patients of whom thirteen were allergic, ten infectious, and seventeen allergic-infectious, with asthma in twenty-six cases. He found that "the Weltman reaction is somewhat more efficient than the sedimentation rate as a diagnostic aid. This is particularly true in borderline cases (as to presence of allergy and/or infection). We believe that these two tests, the Weltman reaction particularly, are valuable aids when determining those patients who have either a primary or complicating infection." Frouchtman,[202] in a study of the sedimentation rates in 160 allergic patients, found the rate slow in seventy-six, normal in seventy-two and fast in twelve. In patients with focal infection slow rates have been found, thus demonstrating that when the focus is allergenic rather than septic the rate is not quickened. Livington[304] has shown that asthmatic children with high sedimentation rates may be greatly benefited by irradiation of nasopharyngeal tissue. All but one of twenty-two asthmatic children successfully treated by radon had elevated rates, whereas of eleven other children who were not helped by this therapy only one had a slightly increased rate. In the successful cases lymphoid tissue entirely disappeared from the nasopharynx and asthmatic attacks vanished, recurred occasionally in mild form, or were less than half as often or as severe as before treatment. These children were under observation for six months to four years, and elevated sedimentation rates returned to normal in all but one of the successful cases.

Wiswell and Rackemann[560] have a long article on chemical factors in asthma, with an extensive review of the literature. They found that: (a) acid-base balance: potential alkalosis is not a constant factor. The poor pulmonary ventilation causes a retention of excess carbon dioxide in the blood with a compensatory rise in plasma bicarbonate level and the administration of hydrochloric acid to such patients increases the excess of carbon dioxide. If this excess cannot be eliminated through the lungs there may be an increase of dyspnea. Administration of alkali only temporarily compensates for excessive carbon dioxide. (b) The sodium potassium and water balance data are confusing. There is no indication that changes in these are specific or fundamental in asthma. Any marked shift in water balance may aggravate or improve asthma. (c) Calcium, phosphorus and magnesium are unimportant in asthma. Any beneficial effects from treatment with these probably results from action on the neuromuscular mechanism. (d) The blood sugar has no relationship. (e) The role of cholesterol and fat metabolism in asthma is not clear. (f) Although deficiencies of vitamin C or niacin probably do not cause asthma they may aggravate existing asthma.

Finlayson[186] has a comprehensive paper on laboratory guides in asthma, especially as regards the importance of eosinophilia in the blood and sputum. Delafontaine and Pistre[150] report that attacks of asthma were accompanied by blood retention of nitrogen in a sixty-five-year-old female observed over many years. In twenty asthmatic patients Serafini and Lauricella[458] determined the potassium

blood level one, two, three and four hours after ingestion of four grams of potassium chloride—the level in asthmatics was 28.5 per cent higher than in normals; levels returned to normal in asthmatics in four hours or more, in two to four hours in normal persons. The presence or absence of an attack did not change results. Serafini and Brozzo[462] also injected 2 c.c. 2 per cent Antergan intravenously; the potassium levels in six asthmatics increased almost threefold as compared with that in six normals, with the highest levels fifteen to thirty minutes after injections. The calcium levels were slightly depressed. Serafini and associates[463] induced fever in asthmatic patients and found a decrease in the alkaline reserve and a decrease in lymphocytes, eosinophiles, and potassium during the fever. Since they found that the fever treatment gave relief they believe that the fever changes symptoms from vagotonic to sympathomimetic. Low blood sugar levels were the most consistent finding in ninety-two patients with intrinsic asthma, say Christensen and Seidel[112]—patients with marked debility, weakness and weight loss. Asthmatic patients may have some hyperinsulinism.

Skin tests are discussed in five papers. Christensen and Sonne[113] believe we rely too much on skin tests, especially with food extracts. One child who was forbidden eggs because of a strong skin reaction subsequently ate three eggs each morning without symptoms. [In our experience such an occurrence has never occurred. We repeat all positive scratch tests if the patients say they are not troubled by the particular food. Almost invariably the repeated test will be negative if the patient is clinically negative; dermographia must, of course, be ruled out.] Pepys[379] also discusses the various types of skin tests, including those by electrophoresis. Tests with foods are not nearly as reliable as with inhalants.

Taub[505] has practically abandoned the scratch test because it is so much less sensitive than the intradermal. He admits that utmost caution must be exercised with the intradermal tests in those sensitive to such potent allergens as cottonseed, linseed, kapok and fish. If the history indicates one of these he advises preliminary scratch tests. [The fallacy of this procedure lies in the fact that, to our knowledge, no cottonseed-sensitive patient has ever suspected this sensitivity until informed by the skin test. Not even an allergist has enough time to ask about possible sensitivity to each and every extract he uses. Why take chances? Too many deaths have followed intradermal testing. The only possible excuses for limiting tests to the intradermal method are sheer unwillingness to do a large number of preliminary scratch tests or a stubborn idea that scratch tests are not worth while. We wish all doubting Thomases would try for themselves the scratch technique with such allergens as egg, fish, nuts, Endo house dust, pollens, fungi, and animal emanations, to mention the most important. We frequently obtain four to six plus scratch reactions to these—and we certainly would not care to do intradermal tests in such sensitive patients. *Intradermal tests should be carried out with extracts which have proved negative by the scratch method.*]

Becker and Rappaport,[55] by the intradermal method, showed "a decrease in responsiveness to the injected allergen as one descends the forearm. The decrease in sensitivity varies directly with the distance down the forearm, with the rate of decrease independent of the concentration in the range of concentrations studied. The decrease between the uppermost and lowermost sites tested on the forearm is equivalent to approximately a 55 per cent decrease in strength of testing dilution. The radial side of the arm was found to be less sensitive than the ulnar, equivalent to approximately a 50 per cent decrease in strength of the testing solution." Zohn[568] found, like most of us, that skin tests with chocolate and cocoa are either negative or give slight reactions despite known clinical sensitivity. [The same is true of milk.]

COMPLICATIONS OF ASTHMA

Involvement of the nose and paranasal sinuses is so common as to be almost a part of bronchial asthma. Rawlins[408] states that allergy is the most common cause of chronic sinusitis; inhalants are usually responsible; the primary treatment should be directed at clearing the allergy, and any infection should be treated conservatively unless otherwise indicated; nose drops should be used with caution. Hyposensitization is used for those inhalants which cannot be avoided e.g. house dust, molds, tobacco smoke and paper. Injections should be stopped when the patient is comfortable; reinject if and when symptoms recur. Darrough[146] says that 75 per cent of rhinological practice deals with nasal allergy; infection may also be present. The allergy is diagnosed by the typical pale, edematous nasal membrane with profuse mucus and sneezing, plus eosinophilia. The presence of polyposis is positive proof of allergy. He never makes more than fifty skin tests for each patient, all intradermal.

Emphysema is almost always present in chronic asthma. Ornstein[369] notes that it differs from other pulmonary and cardiac diseases by impaired diffusion of oxygen and carbon dioxide between the alveolar air and the blood. He analyzed exhaled gases obtained in a 1-liter rebreathing bag in twenty seconds after a standard exercise test of stepping up and down an eight-inch step thirty times a minute. A residual oxygen volume up to 9.5 per cent or lower represents good diffusion of oxygen. Above 10 per cent indicates impaired permeability and diffusion. In addition to this test the ventilatory function is measured with a spirometer for one minute. In a case of lung hypertrophy which compensated for a shrunken, fibrotic, tuberculous left upper lobe healed with pneumothorax, the patient's pulmonary distress was due to poor ventilation; his ventilatory factor was 5.2 (normal 20). Yet his diffusion of oxygen and carbon dioxide was normal. Therefore the decreased ventilation resulted from the destruction of one lung; the hypertrophied right lung, after seventeen years of overactivity, was not emphysematous. Pulmonary function tests are especially important when such surgery as pneumonectomy is being considered.

Castex and his associates[574] produced experimental bronchogenic emphysema in dogs. They were able to reproduce the different stages observed in man, i.e. alveolar dilatation, anatomic emphysema, and ampullary emphysema. These different stages and grades depend more on the intensity of the respiratory obstruction than on the time of its evolution. The greater the obstruction the more severe is the resultant emphysema and the earlier the onset. In addition, the heart of the dog with the experimental emphysema is almost always enlarged, with right ventricular dilation.

Spontaneous pneumothorax is not uncommon in bronchial asthma but Myerson[352] found that asthma was the cause in only three of 100 cases seen at the Boston City Hospital in a nine-year period between 1934 and 1943. Since 375,000 patients were admitted to the hospital in that period, the incidence of spontaneous pneumothorax (all types and causes) was only 0.027 per cent. Of the 100 cases sixty-four, with an average age of forty-six, had some underlying pulmonary disease, of which tuberculosis constituted 59 per cent. Thirty-six cases occurred in apparently healthy persons, with recurrence in three patients, with an average age of only twenty-seven. The symptoms in both groups are about the same, chiefly chest pain and dyspnea. About 20 per cent of both groups gave a history of unusual exertion prior to the acute episode. Aspiration of air to relieve dyspnea was necessary in three cases.

Centrangolo's patient[108] had spontaneous pneumothorax which recurred during attacks of bronchial asthma. He therefore injected 3.0 c.c. Lipiodol and placed the patient on his right side so that the Lipiodol could enter the emphysematous-bleb part of the lung. Adhesions resulted, and although the patient continued to have asthma there has been no further recurrence of pneumothorax.

Dickie, in students seen during four years at the Health Service of the University of Wisconsin, observed twenty cases of spontaneous pneumothorax and pneumomediastinum (mediastinal emphysema).[155] There were six cases of pneumothorax without recognized mediastinal air, seven with mediastinal emphysema alone, and seven with both. In none of these was asthma a factor although an x-ray film suggested emphysematous blebs in one case. Recurrences were rather frequent, and aspirations of air were resorted to for dyspnea or for a prolonged course of symptoms. Dickie gives an excellent description of the symptoms in the fourteen cases with pneumomediastinum, with or without pneumothorax. The onset was usually sudden and varied in severity. Pain was usually "substernal with frequent radiation straight through to the back or into the left neck or shoulder. Pain is associated with change in position or with jarring motion, and six of fourteen patients with pneumomediastinum were aware of peculiar sounds over the precordium. On examination the most characteristic finding in this group is the crunching sound synchronous with the heart beat. This may vary greatly during the episode and with change in position or phase of respiration. The intensity of the sound bears no relationship to the severity of the patient's symptoms; often the patient is almost free of pain when the crunching is most pronounced." Subcutaneous air in the neck or elsewhere was not found in this series.

In a man of fifty-seven with asthmatic attacks for twelve years, Karns and Daue[276] found spontaneous mediastinal emphysema. Cough, pain and dyspnea began suddenly seventeen hours before admission, with swelling of the face and neck and increased dyspnea a few hours later. The face, up to the zygomatic arch, neck, left forearm, both arms, thighs, scrotum, chest and abdomen were ballooned up by subcutaneous emphysema. Crepitus was present and the trachea was deviated to the right; crackling sounds were heard over the precordium during systole and diastole.

Left pneumothorax was also present. The swelling and dyspnea were so extreme that mediastinotomy was carried out under local anesthesia, with escape of retained air and immediate improvement as regards the patient's cyanosis and dyspnea and recovery a little later.

In Klein's case[281] spontaneous pneumomediastinum with fever and leukocytosis occurred in a boy of sixteen. By a series of electrocardiograms right ventricular strain was shown, probably due to encroachment on the pulmonary arteries by air in the vascular sheaths. Subcutaneous emphysema occurred in an eighteen-year-old patient of Mascheroni and his associates.[335] The episode took place during her first attack of asthma. There was no pain and the emphysema disappeared in eight days. Air bubbles were easily demonstrated on x-ray. The authors discuss thirty-four cases previously reported as occurring during attacks of asthma.

Massive atelectasis (massive collapse) is rather rare in asthma [small areas of atelectasis are probably much more common than we can prove]. Huff[266] reports two attacks, complete in one episode, and incomplete in another. The seven-year-old child, with a history of asthma and perennial hay fever since infancy, was first seen in 1932. The massive collapse occurred suddenly in 1944, with shifting of the mediastinal structures to the affected side. Despite the x-ray findings symptoms were unbelievably mild, and there was no fever. She apparently coughed up a mucous plug because an x-ray film ten days later was entirely normal. A second attack occurred eight months later with partial atelectasis of the same side. She was treated successfully with aminophyllin, Adrenalin and inhalations of carbon dioxide.

Spontaneous fracture of a rib occurred in a fifty-nine-year-old asthmatic woman. The pain was on the right side of the neck but the x-ray film revealed a recent fracture of the left first rib. Violent contraction of opposing accessory muscles of respiration probably caused the fracture, says Ginsburg.[220] [We believe that the severe cough present in some asthmatic attacks is the cause and we have recently seen fractures in lower ribs in two of our patients. When one sees the terrific effort used by some patients to expel sputum one would expect even more fractured ribs. Incidentally, such a fracture is covered by accident insurance policies even though it results from asthma.]

Although *coronary* artery disease is infrequent below the age of forty, it caused death in nine of 365 consecutive fatalities, as disclosed by autopsies in an Army Hospital. Death was sudden in each case, says Poe[389] and coronary disease was the only factor. In discussing this case Abramson says "Myocardial disease is not considered to be an early complication of bronchial asthma. Unexpected and unexplained deaths in patients with bronchial asthma below forty are more frequent than is commonly believed. Closer scrutiny of myocardial function in bronchial asthma might reveal hitherto unexpected pathologic lesions in this group." [We do not subscribe to Abramson's opinion; coronary occlusion is uncommon before forty and is probably even less common in asthmatics, possibly because many such patients have learned that tobacco smoke irritates them. We are firmly convinced that heavy cigarette smokers are leading candidates for early occlusion.]

Cor pulmonale is thought by some to result from bronchial asthma as well as from other pulmonary disorders. Spatt,[487] in a study of forty-two cases with autopsy findings, confirms the theory that chronic pulmonary disease is the most important cause of cor pulmonale. The chronic condition destroys and narrows pulmonary capillaries and increases pulmonary artery tension which in turn increases the strain on the right heart; this in turn may result in dilatation and hypertrophy. A study of these forty-two cases disclosed that chronic exertional dyspnea, cough and cyanosis evidently reflected the first stage of the process. Later there followed distension of neck veins, hepatomegaly, edema, ascites and precordial distress. Cor pulmonale is more frequent in men, and death was most frequent between the ages of fifty-one and seventy. An editorial[127] also discusses cor pulmonale and quotes previous work by Scott, Spain and Handler, and Brill. Chronic obstructive emphysema is the main cause and other conditions are less frequent, these including silicosis, bronchiectasis, tuberculosis, bronchial asthma, silicotuberculosis, kyphoscoliosis, and pulmonary arteriolar sclerosis. [It is our impression that cor pulmonale rarely, if ever, occurs in uncomplicated bronchial asthma, no matter how severe, how chronic, or how emphysematous the patient becomes. Every case we have seen has some other condition which is the main or associated factor, e.g. bronchiectasis, kyphoscoliosis or pulmonary fibrosis or tuberculosis. We also believe that left heart failure is extremely rare in bronchial asthma unless the patient has some such associated condition as hypertension, chronic nephritis, aortic regurgitation or coronary occlusion.]

Pulmonary tuberculosis is not a complication of bronchial asthma but the two

conditions can be associated. Van Wezel[532] stresses the importance of controlling allergic bronchial asthma in patients whose tuberculosis needs collapse therapy. The type of collapse therapy will depend a great deal on prevention of attacks of bronchial asthma. He presents ten cases to illustrate the difficulties in the diagnosis of asthma in the presence of tuberculosis, the forms of surgical treatment necessary to control the tuberculosis, and the dangers of such therapy during attacks of asthma.

Cohen[120] reports that bronchial asthma occurred in fifty-five of 7,301 tuberculous patients discharged from Olive View Sanitarium in a ten-year period, an incidence of only 0.75 per cent (lower than that reported among the general population). These two conditions do not seem to predispose to one another although severe asthma seemed to be associated with serious endobronchial tuberculosis. In addition, there are fifteen cases in which the asthma and tuberculosis were present in patients still in the sanitarium. In thirty-eight cases the asthma preceded the tuberculosis and in six cases the reverse was true.

Zeuhn[567] also discusses surgical treatment in such cases. By having the patients high up in the mountains both conditions are so benefited that pneumothorax and thoracoplasty can be successfully carried out. In twenty-six cases of inactive pulmonary tuberculosis with bronchial asthma, Richard[414] obtained good results over a period of a year by injecting very minute dosages of tuberculin. There was no activation of the tuberculosis. Alemany Vall,[14] from Barcelona, contrary to American authors, finds pulmonary tuberculosis very frequent in asthmatic patients—from this he concludes that hypersensitivity to tuberculin causes the asthma, that tuberculin reactions are much more pronounced in these patients than in "simple" tuberculosis, that hypersensitivity to tuberculin causes typical allergic states such as eosinophilia, nasal polyposis, et cetera, before progressing to its usual fatal termination. Dugoujon and Mallet Rene[162] also support Jacquelin's thesis of the tuberculous origin of most cases of asthma, based on the frequency of old quiescent tuberculosis in such patients, of positive tuberculin tests, and of good results from tuberculin therapy. [Despite the higher incidence of tuberculosis in Spain and France as compared with our country one cannot agree that tuberculosis or sensitivity to tuberculin causes true allergic bronchial asthma; any good results from the treatment of bronchial asthma by injections of tuberculin are non-specific.]

Froman[200] has a nice paper on complications of arrested pulmonary tuberculosis. Bronchiectasis, emphysema, bronchogenic carcinoma, and/or atelectasis occur not infrequently in such cases, and the physician may wrongly believe that the tuberculosis has again become active. Wheezing and dyspnea may occur and thus suggest asthma. Kurkijarvi,[289] in a study of 200 cases of pulmonary tuberculosis, found slight eosinophilia in the blood and sputum in many of these. This may be confusing in instances in which asthma and tuberculosis coexist.

BRONCHIECTASIS

The relationship between bronchial asthma and bronchiectasis is still disputed. The two frequently coexist. Mallory,[331] in an authoritative study, summarizes: "Five factors—chronic bronchial infection, congenital abnormalities of the bronchial tree, bronchostenosis, pulmonary atelectasis and pneumonitis or its sequel, pulmonary fibrosis—have been shown to be potential factors in the etiology of bronchiectasis. Of these, congenital cystic disease and bronchostenosis are comparatively uncommon. Bronchial inflammation alone is rarely an effective factor but in combination with atelectasis or pneumonitis adequately accounts for most of the characteristic features of the disease."

Bronchiectasis has four important features: (a) it is rarely diffuse—it usually involves a group of adjoining bronchi; affected segments may be, and frequently are, multiple, but bronchi in uninvolved areas are normal. (b) It is not a progressive disease; there is no extension unless there occurs an attack of pneumonia with involvement of another segment of lung. (c) It is rare as an isolated finding in an otherwise normal lung; the surrounding lung tissue is abnormal, with atelectasis, fibrosis, organized pneumonitis, focal emphysema, or even destruction of alveolar tissue. (d) It usually develops in youth, though it can start at any age. Mallory points out that in bronchial asthma "functional narrowing of the bronchi exists over many years. In a group of sixty such cases that I have personally studied bronchiectasis was so exceptional that it appeared coincidental, although emphysema and cor pulmonale were of common occurrence. Stenosis of bronchi, therefore, does not regularly induce dilatation of the distal branches. If the obstruction is incomplete and expiration is impeded more than inspiration (as in asthma) the alveoli rather than the bronchi tend to dilate, and emphysema results. With complete obstruction atelectasis follows, and this is an important factor in the develop-

ment of bronchial dilatation. . . . It must be emphasized that it is not atelectasis per se that tends to dilate bronchi but the effect of the exaggerated negative intrathoracic pressure, which frequently follows atelectasis. In his fifty cases of bronchiectasis Mallory found emphysema in six but in only one was the emphysema an important cause. "The most hopeful prophylactic measure in the prevention of bronchiectasis is therefore the prevention or prompt alleviation of atelectasis."

Llaudet,[305] from Barcelona, says that congenital defects cause most cases of bronchiectasis; infection, especially tuberculosis, is the usual exciting factor; the prognosis is unfavorable, with resultant disability; hemoptysis is common and causes death in 5 per cent of the cases. Early lobectomy cures 94 per cent of the cases; medical treatment including aerosol is usually unsuccessful. Infante,[268] however, obtained excellent results from penicillin aerosol therapy in a five-year-old girl with saccular bronchiectasis, and success follows intratracheal injections of penicillin, says Thiberge[508] and Loesches.[309] Olsen[366] says resection of the affected portion of the bronchial tree is the best treatment but nebulization helps before lobectomy. When resection cannot be carried out, nebulization (penicillin and/or streptomycin) usually gives some relief, with relapse when inhalations are stopped. Overholt, Betts and Woods[371] discuss segmental resection, a procedure in which infected lung tissue is removed without sacrificing healthy parts.

Singer[472] discusses congenital and acquired bronchiectasis, with tuberculosis the most common cause. Spencer and Kent[488] believe bronchiectasis is next only to tuberculosis in frequency of chest diseases and is often misdiagnosed. It usually begins in childhood, probably following bronchial infections, whooping cough, asthma, pneumonias, measles, scarlet fever, and lung abscess. Sinus disease is a factor. In a photoradiographic survey of 156,000 candidates for flight training, Steinhausen and Fine[491] found forty-one cases of unsuspected bronchiectasis. Wearing[554] reports forty-six cases of bronchiectasis in 214 patients whose symptoms suggested chronic bronchitis, with a past history of pneumonia in twenty-six. Clubbed fingers were present in eight cases, and Poppe[392] says clubbed fingers occur in about 80 per cent of cases with severe bronchiectasis and chronic lung abscess.

Surgical aspects of bronchiectasis are discussed by Naef,[354] Allan,[10] Streider,[498] and Valledor and Rodriguez Dias.[525] Badger[44] points out, however, that in 400 cases of bronchiectasis treated in the Massachusetts General Hospital, 59 per cent were unsuitable for surgical treatment. For these and for those who refuse surgery or have little or no symptoms, medical management is necessary, e.g. mechanical drainage, control of infection, measures to improve the general health and the prevention of bronchiectasis. Biering[65] and Averbe[41] also discuss this condition, and Schmidt,[445] Gann,[213] Dell[151] and Blaisdell[71] give the technique and indications for bronchography.

Carr, Denman and Skinner[102] report that forty-six of 144 workers in a gas (mustard) shell loading plant developed moderate to far advanced bronchiectasis, with minimal symptoms in forty-one or more. Asthmatic bronchitis was present in forty patients, and eleven had bilateral emphysema. By removing these patients from contact with mustard gas, plus medication, good results were obtained in almost all cases except in those with emphysema.

DIFFERENTIAL DIAGNOSIS OF BRONCHIAL ASTHMA

When a patient is referred for "asthma" we must prove that bronchial asthma is or is not present. We have recently had cases in which the "asthma" was due to sighing dyspnea, substernal thyroid, carcinoma of the trachea, cardiac disease, or silicosis. The differential diagnosis and management of bronchial asthma is outlined by Unger,[523] along with a table giving the differential points between bronchial asthma and "cardiac asthma," also a discussion of two patients with asthma and another one whose dyspnea was due to byssinosis, a condition akin to pneumoconiosis. This patient stuffed loose, raw cotton into quilted robes and inhaled some of the cotton. X-ray films revealed a diffuse mottling throughout both lungs, due to fibrosis, and the patient had fever for about a year.

Sweany and Thompson[502] outline laboratory methods useful in the differential diagnosis of chronic chest diseases, e.g. the sedimentation rate, the increase in serum globulin so characteristic of sarcoidosis, the differential blood count (often neglected) cultures of the sputum, stomach washings, pleural fluid, bronchial aspirations, biopsies, animal inoculations, micro-sections, and skin tests with tuberculin, histoplasmin and coccidioidin. Smart[476] and many others emphasize the importance of mass chest surveys of apparently healthy groups, chiefly to pick up cases of pulmonary tuberculosis.

Adenoma of the bronchus is not rare and may cause dyspnea and wheezing

and thus be confused with bronchial asthma. Naclerio and Lange[353] find this tumor in about 80 per cent of the benign bronchogenic growths. Symptoms are rare at first but a dry, irritating cough follows. Hemoptysis is a cardinal symptom, and symptoms from partial or complete obstruction of a bronchus may or may not occur. The diagnostic procedures include plain and section roentgenography, bronchography and, best of all, bronchoscopy. Ten patients were cured by pneumonectomy and five by lobectomy. Souders and Kingsley[481] review the literature and present fifteen cases of their own; these were found among 217 histologically proved primary lung tumors encountered at the Lahey Clinic since 1930, an incidence of 6.9 per cent. Adenomas can usually be diagnosed bronchoscopically; they are potentially malignant but the malignancy is of low grade. Sixty per cent occur in patients less than forty years old. Resection of the tumor and infected lung tissue is advised but pedunculated adenomata may be removed alone. Fried[194] also emphasizes that a bronchus adenoma is benign, occurs in bronchi whose diameter is at least 10 mm., grows into the lumen or the parenchyma of the lung, and may cause cough, wheezing, hemotypsis, and recurrent symptoms like pneumonia if obstruction occurs.

Holinger, Andrews and Anison[262] discuss pulmonary complications due to *endobronchial foreign bodies.* "In a series of 1026 consecutive cases of foreign bodies in the air and food passages (in eleven years), 353 or 32 per cent were found and removed from the tracheobronchial tree. Pulmonary complications depend upon the location, sojourn, and character of the foreign body. Vegetable objects (peanuts, corn, beans, twigs, grass heads, etc.) produced the most severe acute inflammatory processes and were often overlooked as the cause of the disease. Metallic objects (tacks, screws, parts of toys, safety pins and common pins) were not as frequently the cause of severe acute pulmonary infections, but were more often responsible for extensive bronchiectasis, severe hemoptysis, empyema, and pneumothorax when they remained in the bronchi for weeks, months or years. . . . The individual complications consisted of 'asthma,' emphysema, pneumothorax, atelectasis, bronchiectasis, lung abscess, and empyema. Two fatalities (0.6 per cent) in the 353 cases of bronchial foreign bodies are recorded." They emphasize the importance of a careful history and examination, including x-ray and endoscopy. A history suggesting foreign body is invaluable but a negative history is valueless and misleading. Early discovery and removal of foreign bodies lessen serious complications.

Peanuts are especially dangerous. Bonnier[77] removed them from the lower respiratory passages of forty-five patients (forty-three children), with death in five cases. Ages in children ranged from eight months to ten years. In thirty patients (66 per cent) there was a definite history of choking on a peanut. Three out of four peanut kernels were found in the right bronchus, with only seven found in lower lobe bronchi. A child's life is endangered when it is very young, or when the peanut is large or obstructs high up; in such a case death can be quick. A small piece low down can give few signs and symptoms occur more slowly. In many of the cases the x-ray films did not show the peanut even when present. The symptoms are not always classic. Only a slight cough or wheeze may occur, but an "asthmatic wheeze" was present in almost every case. Huff's 3-year-old child[265] wheezed on expiration for six months. A tentative diagnosis of bronchial asthma was made, but removal of a long roofing tack from the right main bronchus solved the case. Edema of the walls of the bronchi and tenacious exudate around the tack simulated bronchial asthma.

Tumors of the lung are discussed by many. Pool[391] discusses carcinoma and emphasizes the importance of such symptoms as hemoptysis, cough and pain, and the findings of consolidation, atelectasis, and/or localized emphysema or pleural effusions. Wheezing or persistent rhonchi over one area is always suggestive of partial bronchial obstruction, especially when associated with prolonged expiration. If these findings are repeatedly present a growth is probably present, not a mucous plug.

In addition to those papers already discussed in the section on bronchiectasis, Clerf[117] notes progress in the science of bronchology. Less than 2 per cent of all bronchoscopic procedures are now performed for foreign bodies, as compared to about 25 per cent in earlier years. Bronchopulmonary diseases, including bronchial asthma, now far overshadow foreign bodies as causes for bronchoscopic study and therapy. In addition to its value in differential diagnosis of asthma, Clerf correctly says "studies of fatal cases of status asthmaticus have shown that one of the most common and important causes of death is the blocking of the larger air passages by thick, tenacious secretion. Failure to secure a satisfactory response by the accepted methods of medical treatment in cases of marked dyspnea due to accu-

mulated secretions necessitates that these be mechanically removed by bronchoscopic aspiration. Spectacular results have been secured at times in moribund patients. It is obvious, of course, that in cases of this type little can be hoped for unless the life-saving measures are employed by one well qualified; for among bronchologists it is admitted that two contraindications to bronchoscopy are an inadequate armamentarium and a poorly trained bronchologist." [We say "Amen"] we at Wesley Memorial Hospital are fortunate in having the services of an excellent bronchoscopist for both diagnosis and treatment. We are sure that he has saved the lives of several of our patients.]

Broyles[91] discusses bronchoscopic experiences with tumors of the lower respiratory tract. Holinger[261] points out that both bronchial asthma and emphysema may closely simulate other diseases in which bronchial obstruction occurs. Even more significant is the frequency with which a true obstruction is considered simple bronchial asthma. The confusing factor is usually the "asthmatoid" wheeze caused by the obstruction, yet it differs from the wheezing in bronchial asthma because in the latter cough usually changes the wheeze and the wheeze is usually louder on expiration. The wheeze of obstruction is uninfluenced by cough and is usually inspiratory. Bronchoscopic examination usually helps in differentiation. Holinger's endoscopic photography in this and related fields should be seen by all.

Epstein, Sherman and Walzer[175] note that bronchography may be greatly facilitated by injections of epinephrine. In sixteen asthmatic patients attempts at bronchography without epinephrine were unsuccessful. Spasms of cough occurred as iodized oil was instilled and the oil was either expectorated or swallowed; under fluoroscopic observation no oil entered the swollen bronchi. But when 0.5 to 1.0 c.c. of 1:1000 epinephrine was injected subcutaneously the secondary bronchi relaxed within thirty seconds and the oil could be seen entering and outlining the bronchial tree. Little discomfort occurred, and good grams were obtained in fifteen of these sixteen patients, with radiologic evidence of bronchiectasis. The entire technique of the procedure is outlined.

TROPICAL EOSINOPHILIA, LOEFFLER'S SYNDROME, PERIARTERITIS NODOSA

Confusion still exists in differentiating these three conditions. Eosinophilia is usually much higher than in bronchial asthma. Wheezing and dyspnea are often present.

As noted in our last review[521] Wilson[559] found seven cases of *tropical eosinophilia* in East Africa in thirty-four natives with chronic cough or wheezing. All were sick less than three years, and all had leukocytosis with pronounced eosinophilia. Six were completely relieved by intravenous injections of arsenic; one cleared spontaneously. Symptoms usually continue until the specific arsenical is given, whereas in Loeffler's syndrome the cough, fever, eosinophilia, leukocytosis, and pulmonary consolidation usually clear spontaneously in about eight days. Wilson therefore does not believe the two conditions are the same. Coutinho,[134] from Brazil, reports five cases of tropical eosinophilia. In two there seemed to be a relationship with infection (amebiasis). As previously stated[54] Telles[507] gave the first report from Brazil.

Loeffler's syndrome continues interesting. Loeffler, who first described the syndrome (1932), and his co-workers[307,311] say that the picture of transitory lung infiltration, with fleeting blood eosinophilia, is benign. Ascaris infestation is the main cause, they say, and in their cases Ascari were found in the intestinal tract in 23 per cent and within 4 to 6 weeks after the lung infiltration became manifest. Other factors are rarely responsible. In forty-eight guinea pigs they demonstrated the causal significance of ascariasis. They reproduced in every detail the syndrome of evanescent pulmonary infiltration, and demonstrated the larvae of Ascaris in eosinophilic infiltrations, thus confirming observations made by von Meyenburg and Nagel in the human. They emphasize atelactasis as a cause of the infiltrations.

Von Heni and his associates[539] review fifty-six cases, forty of which occurred in about a year. Their work with animals and patients confirms the importance of Ascaris infestation. The outlook in all cases is good, and the treatment is "worm cure." Clark and Rosenberg[115] studied a four-year-old boy admitted to the hospital because of a second tonic seizure of the upper extremities. There was no history of allergy, and blood eosinophilia was 4 to 12 per cent. X-rays showed typical migratory lesions. Ova of Ascaris lumbricoides and Trichuris tricuria were found in the stools, a skin test was positive for Ascaris, and anthelmintic treatment was followed by improvement after four weeks.

Bertrand-Fontaine and associates[64] report two cases in young women, both severe, with widespread pulmonary involvement. Two months after onset Ascari were

found. The authors believe that the pulmonary manifestations result from the direct action of the worm in its migratory stage in the lung; they do not think the condition is allergic, not even to Ascari at distant sites. This concept is supported by the facts that (a) larvae are not found in sputum during acute pulmonary symptoms; (b) in the two cases cited the recovery of adult Ascari in the stools coincided with the expected time in the life cycle after the pulmonary migration.

O'Bryne[363] says Loeffler's syndrome is almost certainly an allergic phenomenon. While infestation by Ascaris is important in many cases, it cannot be the sole or even the main cause, at least in this country. Pollen, bacteria, viruses, amebae, and other factors may be responsible. In O'Byrne's 5-month-old girl the eosinophilia ranged from 4 to 50 per cent. There were no respiratory symptoms at that time, but in the last seven years there have been occasional attacks of asthma. The case report contains six excellent roentgenograms.

Ham and Zimdahl[234] review the literature and add three cases. One had a long, stormy course which did not resemble typical Loeffler's syndrome. In another, symptoms suggested angina pectoris. Only the third patient had a definite hypersensitive background and in none was the cause found. Squier[489] also reports three cases. In one of these, early fleeting infiltrations occurred but repeated attacks have left increasing residual fibrosis and evidence of irreversible damage. This irreversibility seems more common in so-called intrinsic or bacterial sensitivity. Single cases are reported by Pearlman,[375] Williams and Walker,[558] Rice and Scott,[413] and Dallas.[143] In a forty-two-year-old patient of Henderson and Pierce,[250] the usual transitory shifting pulmonary shadows and pronounced fluctuating blood eosinophilia were present. In addition to sensitivity to house dust and ragweed pollen, the patient was also allergic to the infecting organism, Hemophilus influenzae, which was constantly found in the sputum and infected sinuses. Later, on readministration of the specific vaccine, there developed joint and muscle pains, fever and purpura of the Schönlein type, and a transitory bundle branch block. This indisputable evidence of vascular allergy corroborates the view that the Loeffler shadows are due to allergic edema of the interalveolar pulmonary tissue with its widespread capillary connections.

Font[189] considers Loeffler's syndrome merely a variation of tropical eosinophilia. Wheezing occurred in his second patient, and both patients had transient pulmonary infiltrations and high blood eosinophilia. He attaches much importance to the fact that he isolated pure cultures, chiefly streptococcus viridans, from sinuses of both. A case reported by Elkeles and Butler[173] is unusual in that a 19-year-old soldier showed a transient apical cavity as well as recurrent pulmonary infiltrations, along with eosinophilia in blood and sputum. There was no tuberculosis. The great variety of antigens causing this syndrome indicate that it is not a specific entity but rather a manifestation of allergy in which the lungs are the main shock organs.

Interesting are five case reports by Diaz Rivera and associates.[154] Because of eosinophilic infiltration of the lungs he makes the diagnosis of Loeffler's syndrome—yet rapid and striking improvement followed therapy with arsenicals. [Here, then, we see further reason for the confusion which exists in nomenclature. Arsenicals are practically specific in tropical eosinophilia, not in Loeffler's syndrome. Such reports as these emphasize the close relationship of these two diseases.] Berman[59] discusses Loeffler's syndrome in children, and Pedrazzini[375] finds that the most frequent cause is intestinal taenia. De Martini[152] differentiates lung cysts and Loeffler's syndrome; he believes that tuberculosis is usually responsible for the syndrome. Lehmann[293] has an interesting paper with a case report of a man with both Loeffler's syndrome and erythema multiforme. He reviews the literature on the syndrome, tropical eosinophilia, creeping eruption, and eosinophilic granulomas of the skin. He also tabulates the causes of eosinophilia.

Periarteritis nodosa is reviewed by Laipply.[290] The entire thickness of vessel walls may be affected. Localized thickenings of arterial walls with aneurismal formations may lead to nodular swellings (nodosa). Hemorrhages ranged from petechiae to extensive. Rupture of aneurisms may be fatal. Microscopically: there is edema, degeneration, necrosis, exudation in all coats of the vessels. Clinically: there are two groups: (a) those with an acute infection with toxemia, and (b) those with circulatory disturbances from the arteritis, depending on involved sites. Course: this is usually fatal, but recoveries have been reported. Duration: this is from weeks to months, infrequently years. Etiology: this is unknown; allergy thought to be a factor.

Goodman's 17-year-old patient[226] recovered after an attack of periarteritis nodosa which probably was due to ingestion of 4 grams daily of sulfadiazine for about a week, given for a sore throat. Recovery occurred but the sore throat returned

in six weeks, and after another two days of sulfadiazine he became very ill and stopped the drug. Fever, purpura, prostration, and other symptoms followed. Biopsy of the deltoid muscle showed periarteritis nodosa. The boy was very toxic and a house physician, apparently unfamiliar with the patient's history of sulfonamide sensitivity, resumed therapy with sulfadiazine, one gram daily. Generalized urticaria developed, relieved by epinephrine and the diazine was continued for five days. Improvement and recovery, strangely enough, followed. Skin tests two years later were negative, and no clinical symptoms followed ingestion of 2 grains of the diazine. In this case recovery seemed to follow a severe prolonged anaphylactic reaction produced by the unwitting administration of the drug at the height of the patient's illness.

A 51-year-old female patient of King[282] is still living after symptoms for perhaps ten years. Since her discharge from the hospital her weight has increased from 93 to 129 pounds, with no fever for about a year. But blood eosinophilia and tender skin nodules persist. Asthmatic symptoms and chronic sinusitis preceded the onset of the periarteritis nodosa. No definite etiologic factor other than allergy was found.

Recovery is reported by Miale, Doege and Piehl[340] in a 40-year-old man, despite gangrene of the ileum, acute renal damage and allergic dermatitis. The arteritis was diagnosed early and medication was stopped, with recovery. A second patient, aged sixty-seven, showed marked periarteritis nodosa on autopsy, with most severe involvement in the kidneys and liver. The authors are sure that the relationship between hypersensitivity and acute arterial disease is more than accidental. Definite atopy was present in both men. Madison[329] discusses the pathology of this condition and three cases in which the occurrence of hemorrhage was invaluable in early antemortem diagnosis. In Case 1 the bleeding was into the skin and from the lungs and intestines; the lungs and stomach were involved in Case 2, and the stomach, skin and kidneys in the third patient. A 62-year-old male patient had no allergic manifestations until twelve months before his final illness, say Shepard and Phillips.[328] Then "asthma" occurred, followed by serosanguinous nasal discharge, profuse perspiration, pain, paresthesias, eosinophilia, wasting and terminal hemoptysis; autopsy confirmed an earlier diagnosis of periarteritis nodosa.

PULMONARY DUST DISEASES

Diseases due to inhalation of various dusts must also be differentiated from bronchial asthma. *Silicosis* is discussed by several writers. Yegge[565] says roentgen supervision is necessary for all exposed. Susceptibilty is increased if ciliated epithelium has been injured by infection. The hazard of silica dust varies with size of particles, number per cubic foot of air, free or combined state of silica, humidity, and length of exposure. Engineering control is best, but difficult and expensive. The most harmful particles are 1 to 3 microns in diameter; those over 10 microns have no effect. [This fact is also pertinent in the size of particles used in aerosol therapy, as with penicillin.] Damage begins when dust containing 70-80 per cent silica exceeds 5,000,000 particles per cubic foot. The risk of complicating tuberculosis is increased with excessive humidity. Dyspnea, cough, expectoration, bronchitis, and emphysema are common, thus simulating asthma. Death usually occurs from tuberculosis or rather sudden cardiac decompensation. Yegge likes Garland's classification of silicosis: incipient, interstitial, nodular, and conglomerate.

Yegge says that aluminum hydrate directly inhaled or dispersed in dressing rooms before exposure may inhibit the pulmonary effect of silica. Berry,[63] in a study of twenty-six silicotic patients who were treated with inhalations of aluminum dust and nine patients who received no aluminum, could find no definite difference between the two groups. Most of the patients in both groups reported subjective improvement. But there is evidence that the treatment itself may be harmful;[20] aluminum in certain physical states may cause pneumoconiosis. Dernehl[153] favors the aluminum treatment of silicosis; there are now 102 treatment units in the United States with a high percentage of reported improvement. He believes that the pulmonary symptoms in silicosis are due to bronchospasm, not to toxicity.

Roche and Ode,[422] in the Lyon-Saint Etienne district of France, state that the emphysematous lesions accompanying silicosis can be strikingly demonstrated by a post-mortem radiologic technique. They believe that the severe dyspnea, out of all proportion to the clinical x-ray evidence, and the inefficiency of treatment are due to extensive emphysema. In Switzerland, says Nicód,[360] exposure sufficient to cause silicosis may vary from a few months in a mine to as much as thirty-four years. In 100 miners, seventy-seven exhibited their first symptoms less than ten years after they quit the mines, whereas twenty-three others lived a nor-

mal life for more than ten years in a dust-less environment before dyspnea and bronchitis occurred. Tuberculosis occurred in seventy-one of 117 cases.

Byssinosis (inhaltation of cotton) is mentioned above by Unger,[523] and Dernehl[153] says repeated prolonged exposure in cotton workers causes chronic irritation of the respiratory tract, with "asthma" in some. Allergy to cotton protein may occur, as proved by direct skin tests and by passive transfer.

Bagasse lung disease may not be due to inhalation of particles of bagasse fiber (sugar cane from which the sugar has been extracted) say Gerstl, Tager and Marinaro.[218] Lesions in experimental rabbits did not resemble human bagasse disease nor silicosis. Bagasse is stored for months to years, broken and pressed into such building materials as Celotex. It is thought that fungi cause deterioration of the fibers and that inhalation of these fungi causes the disease. Le Mone and his associates[294] point out the seriousness of the condition. About two months of exposure are required before symptoms occur, with fever, severe dyspnea, persistent cough, scanty mucoid sputum, and profound weakness. The onset is insidious. The exact etiologic basis is obscure although it occurs only in exposed persons. Radiologically, diffuse infiltration and consolidation, acute bronchiolitis or pneumonia may occur, but, fortunately, the condition is reversible, with resultant resolution and return to normal, provided, of course, that exposure is terminated.

Beryllium caused delayed pneumonitis in twelve men and twenty-four women who manufactured fluorescent lamps, says Hardy.[243] The material used to coat these tubes is a mixture of zinc, manganese and beryllium silicate. Onset of symptoms is gradual, with weight loss, fatigue, increasing exertional dyspnea, anorexia and nervousness. The dyspnea may become ceaseless, and in two the diagnosis was confirmed by autopsy. Of the thirty-six patients, twenty-three are still functionally disabled, twelve completely and eleven partially, and this after an average illness of two years. There is no satisfactory quantitative test for this chemical in the air, but the disease developed in two persons who lived close to the building where the fluorescent powders were being handled; they did not work in the plant. Pascucci[374] discusses the clinical, autopsy and radiologic findings in thirty-two patients. No other disease produces the characteristic fine, disseminate, granular type of infiltration of the lungs, as shown by x-ray. Both the granular and the nodular types may occur, and the prognosis is worse in those with the granular type of nodulation, especially when confluent shadows are superimposed. Roentgenologic changes, however, may exist without significant symptoms.

Siderosis (caused by inhalation of iron fumes) is a rather benign form of pneumoconiosis, with deposits of the metal dust in the lungs. Sander[442] reports three cases with (a) discrete and rather sharply defined rounded shadows of more or less uniform size and equal distribution in both lungs; (b) no tendency to confluence; and (c) hilar shadows always smaller than would be expected with silicosis of this degree. Gross black pigmentation at necropsy has been erroneously diagnosed as anthracotic, whereas a ferrocyanide stain would have revealed iron. Gross round lesions also have been incorrectly called silicotic without use of the connective tissue stains to determine true fibrotic nodules.

Asbestosis, another pulmonary inhalation disease, is discussed by Riddell.[415] It is due to fibrous silicate and lung fibrosis may occur, with a ground-glass appearance on x-ray. Cardiac symptoms are common. Riddell also states that inhalations of *Cadmium* (fumes or dust) can cause severe damage, with dyspnea, persistent cough, cyanosis, and prostration; a chemical pneumonia can occur. Lung disease can also occur from inhalation of *arsenic* and certain *radio-active substances*. Riddell discusses the factor of compensation in pneumoconiosis. Dernehl[153] says inhalation of *sulfur* is a rare cause of industrial disease in the United States, and the incidence of tuberculosis in *cement* workers is only 0.18 per cent as compared with 1.0-1.5 per cent in the general population; the general health in the cement industry is very good, and silicosis occurred in only six of 1,979 workers.

PULMONARY CYSTS AND BULLOUS EMPHYSEMA

These two conditions, perhaps the same, may be confused with bronchial asthma. Adams[7] has a fine article on the pathologic characteristics and importance of congenital lung cysts, based on a study of twenty-seven patients, in twenty-four of whom symptoms occurred only after the cysts had become infected. In several cases treatment for over a year had been carried on for other conditions, e.g. bronchiectasis, lung abscess, empyema, or tuberculosis. Nine other authors have reported similar experiences in twenty-six collected cases. Diagnosis is difficult because of similarities in the clinical course. The x-ray, with fluoroscopy, remains best for correct diagnosis, but must be correlated with the clinical findings. Since

the risk of operation is small, resection of the involved lung is the treatment of choice.

Solitary lung cysts were removed by Anderson[23] in twelve patients, with death in three; the survivors remain well. McRae[324] reports death from congenital lung cysts in four of eleven children in a French-Canadian family. This family incidence is unique, in that marked clubbing of fingers and toes occurred without pulmonary sepsis, yet the four children succumbed early in life. Ashen-grey pallor, without actual anemia, was present; cyanosis did not occur; dyspnea on exertion, frequent "colds" with cough and sputum and râles were present. Expiratory wheezing was widespread in one case, with the diagnosis of lung cyst confirmed by autopsy. Wheezing may dominate the picture so completely that nothing else can be made out. But repeated x-rays reveal steady progress of the cystic nature of the condition.

Korol[287] believes emphysema is a form of lung atrophy due to inadequate blood supply. Post mortem the anemia is striking, and histologically there is an obvious disappearance of capillaries. In a study of 100 cases of advanced bullous and cystic types of emphysema, allergic bronchitis and asthma were present in twenty-three cases, with progressive emphysema. Infection occurs in the bullous type, says Korol, but not in the cystic form. Silversides[470] reports two cases of giant bullous emphysema in upper lobes. In one case great improvement followed lobectomy. Two cases of bullous emphysema associated with asthma and tuberculosis are reported by Lowance and associates.[314] They also discuss the differential diagnosis of bronchial asthma from asthma complicated by an omental hernia through the foramen of Morgagni into the right lung between the first and second lobes; intrinsic asthma with a superimposed cardiac asthma; and carcinoma of the lower bowel and wheezing due to metastases to the lungs.

FUNGUS INFECTIONS OF THE LUNG

These are probably much more common than we can prove. Smith[478] differentiates between coccidiomycosis and histoplasmosis. The skin tests are usually accurate, and identification of the respective fungus clinches the diagnosis. Dickie and Clark,[156] in a routine survey of 5000 students by photofluorograms and by tuberculin testing, found pulmonary calcification and negative tuberculin tests in 160. In sixty-six of seventy-three of this group this calcification was associated with postive skin tests to histoplasmin. It is therefore evident that a diagnosis of tuberculous infection made solely by x-ray is frequently wrong. Histoplasmosis can cause both calcification and infiltration.

In ten of seventeen patients ill with pneumonia in Camp Gruber, Oklahoma, Mickle[342] was unable to identify the cause. In ten of these C. Albicans was isolated but there was no other evidence to support its etiologic role. Moody[349] reports death in a Mexican laborer admitted for pulmonary tuberculosis, but with negative sputa. On bronchoscopy a fungating tumor mass was found below the larynx. Sections of cystlike masses and smears of mucinous bronchial material contained many encapsulated organisms characteristic of Cryptococus neoformans (Torula histolytica). Autopsy was negative for tuberculosis; areas of silicosis were found. Penicillin and sulfonamides failed to help. Kay[278] writes on actinomyces in bronchopulmonary infections. The organism itself is commonly found in such infections (found in the sputum of 109 of 240 patients). Actinomyces were always found in mixed infection, but are probably clinically significant only under anaerobic conditions.

MISCELLANEOUS CONDITIONS WHICH MAY CONFUSE

Riley has a nice differentiation between cardiac and pulmonary dyspnea, one of a series of pamphlets published by the American Heart Association.[416] "Dyspnea is a manifestation of ventilatory insufficiency which may be caused by certain types of pulmonary or cardiac disease. A reasonable estimate of the contributions of each disease to the dyspnea can be made on the basis of characteristic physiologic abnormalities." He discusses the clinical symptoms of each, and various tests. In cardiac asthma, says Chapman[109] the râles are usually inspiratory, in bronchial asthma usually expiratory and sibilant. In bronchial asthma the entire costal margins move medially on inspiration; in cardiac asthma the median costal margin moves medially and the lateral ones laterally. Bizzozero[68] says cardiac dyspnea cannot always be differentiated from bronchial asthma. Crystal, Edmonds and Betzold[139] report a case with a symmetrical *double aortic arch*. The vascular rings encircle the trachea and esophagus and cause difficulty in respiration and in deglutition; there is a fairly characteristic syndrome with stridor, wheezing, crowing, bouts of cyanosis, dysphagia, regurgitation and recurrent respiratory infections.

The patient was eight weeks old, with wheezing and dyspnea since birth. There were periods of unconsciousness lasting from thirty seconds to ten minutes. Convulsions occurred at the age of ten, with distention of superficial veins of the neck and torso. The correct diagnosis was made, aided by the x-ray, but the child died during the operation; right and left aortic arches tightly embraced the trachea and esophagus.

Bishr's[67] ten-year-old boy had a huge right-sided pulmonary hydatid cyst which caused spasms of cough, dyspnea and wheezing, with some relief from ephedrine. There were 15,200 luekocytes with 14 per cent eosinophiles; the eosinophilia, however, lost most of its significance when ascaris ova were found in the stools. The Casoni skin test, using fresh fluid from a hydatid cyst, was strongly positive, and the sac was shelled out with no further asthmatoid attacks. No one knows exactly why this cyst led to attacks of "asthma."

Villafañe Lastra and his associates[536] describe patients with brucellosis in whom asthmatic symptoms occurred, varying from recurrent mild crises to severe status asthmaticus. When the diagnosis of brucellosis was established, aided by a Huddleson positive reaction and strongly positive intradermal reactions to Melitin, injections with Brucella abortus vaccines relieved the respiratory symptoms. The authors believe that a possible hapten of the Brucella toxin combines with pollen, dusts or foods to cause sensitization. They recommend routine investigation for Brucellosis, in addition to the usual allergy tests.

Becker[56] suggests that "heaviness of the chest" and/or a chronic cough may preceed true asthma. In such cases the family history, eosinophilia, and relief from such drugs as epinephrine or ephedrine will aid in the correct diagnosis. Bernton's[61] seventy-seven-year-old female patient sought relief from an allergist because she had acute attacks of nocturnal dyspnea along with generalized hives, duration four years. Slight wheezing was noted. Skin tests had been carried out at the onset, were positive for house dust, and she had received aminophyllin and epinephrine. Significantly, she said, she had a "clutching feeling" below the left breast after dinner was down only a minute. An x-ray revealed that the esophagus was deviated toward the right in its lower third due to a large hiatal hernia of the stomach. Because of her age, operation was not carried out. Bernton says no real asthma existed but the dyspnea was almost certainly due to direct pressure by a distended stomach on lung tissue. Small, frequent meals were prescribed.

"Asthma" following a primary carcinoma of the pancreas is reported by Swiegert, McLaughlin and Heath.[503] At autopsy two months later this twenty-two-year-old patient showed diffuse metastatic involvement of the lungs, bronchial lymph nodes, liver, adrenals and vertebrae. Walker and Gann[546] report two cases of edema of the larynx complicating epidemic parotitis (mumps); such an occurrence may be confusing.

Neurocirculatory asthenia (effort syndrome) may lead to tachypnea and dyspnea, probably due to some essential irritability or stimulation of a center or centers within the central nervous system, this causing respiratory manifestations. Friedman[199] describes a new hyperventilation test, preceded and followed by maximal breath holding. The range of the H. I. (hyperventilation index) is about the same in normal persons and in patients with intrinsic pulmonary or cardiac disease, but without neurocirculatory asthenia. But those with this asthenia, with or without cardiorespiratory disease, always have a low H. I. Friedman discusses sixteen patients with respiratory symptoms due to hyperventilation. Attacks begin when the patients feel they are not getting enough air; so they breathe deeply and rapidly with a sigh during expiration; this leads to tachycardia and, in some cases, extrasystoles may occur. The hands and feet are usually cold and tremulous; excessive perspiration is common, along with vertigo, sharp precordial pain and tingling of the hands and feet. Carpopedal spasm occurred in three cases. Friedman emphasizes the fact that attacks can and do occur at rest, not always due to effort. [This is an important diagnosis, similar in many ways to "sighing dyspnea," but with an even greater psychic involvement. We have seen similar cases in which wheezing and dyspnea occur in patients who have a strong emotional personality; in such cases search for causative allergens is almost always ineffective even though their wheezing strongly suggests bronchial asthma. Relief occurs solely from psychotherapy. A recent example is a man who has been under our care for "asthma" for over a year. His attacks of dyspnea and wheezing were relieved by epinephrine and aminophyllin but he lost weight, morale and strength till he became an invalid and was dependent on his wife. Separation from his wife by transfer to a sanitarium has effected a remarkable improvement with almost total disappearance of his "asthma." In other words, this man probably never had real allergic asthma—he had psychogenic symptoms for over a year.]

THE TREATMENT OF BRONCHIAL ASTHMA

Specific treatment continues to be neglected. Perhaps we have reached the stage in which specific avoidance, with or without hyposensitization, is accepted as the best treatment for patients with bronchial asthma. But we doubt the correction of this assumption. Some of us, we hope the majority, still try to find the cause of attacks and to remove or combat in a specific manner. But many physicians, including a few allergists, have become so interested in the newer drugs that they have not clung to the narrow but most fruitful measures, those which are specific and which undoubtedly give the best results. All other measures—and they are legion—can only give temporary improvement. The new agents must not be neglected—some are valuable, but they must not supplant those which have been successful.

Branderberg and Wilander,[80] from Sweden, discuss desensitization in twenty-eight allergic children, chiefly asthmatic. They obtained better results with extracts prepared from surroundings close to the patient. They made some extracts which seem unusual to us, e.g. birch leaves and catkins, hazelnuts, boiled and raw milk, cooked and raw egg yolk and egg white, and sawdust. Injections are raised till the child tolerates 1.0 c.c. of the undiluted extract; they usually reach this dosage in eight to fourteen days and then the injections are repeated monthly for one year. No deaths occurred. Sixty per cent gave positive skin tests to house dust, and about one-third to horse, cat and/or cattle danders. The results were excellent in nineteen (76 per cent) of twenty-five patients and poor in six (24 per cent). There were no complete recoveries. One child developed angioneurotic edema to fish and horse dander extracts but persistent injections once a month led to good results. The authors are favorably impressed by this specific hyposensitization and urge its use before the condition becomes chronic. Glaser,[223] commenting, says this method of treatment is "at such variance with the common experience in this country. Hypodermic desensitization is almost never practiced to foods in this country. The feeling among pediatricians, and this is commonly borne out by experience, is that if the child refrains from eating a particular food, he will eventually, even though it may take several years, lose his sensitivity to that particular food. Hyposensitization to foods by the method of injection is considered extremely dangerous and exceedingly time consuming, and scarcely worth the risk and effort."

[We agree with Glaser that allergy to foods diminishes with avoidance, and that hyposensitization to these foods by the hypodermic method is rarely necessary. But Glaser did not mean that avoidance will eventually bring loss of sensitivity to all foods. Those who are highly allergic to fish, eggs, or nuts almost certainly remain sensitive to those foods. Hyposensitization (oral or hypodermic) will lessen the sensitivity in most patients, and is no more dangerous than with such a potent allergen as horse dander. We have given injections of egg white extract to many children because of extreme sensitivity to egg, and have been rewarded by an increase in tolerance to the point where the patient can eat egg-containing foods or even a little cooked egg. We also inject wheat-sensitive patients; they obtain results much more quickly unless their exposure is overwhelming. We do not give injections of any other food extracts as these other foods are not essential. We would hyposensitize for milk if we could find or make a good extract.]

Henriksen[253] made a follow-up study of 100 asthmatic patients who had received specific desensitization three years previously. Remarkable improvement was still present in 59 per cent, but 16 per cent of these claimed that factors other than desensitization caused the improvement. The final figure is therefore 43 per cent.

TREATMENT OF ASTHMA BY DRUGS

Rackemann[403] has such an excellent editorial that we quote it in full. He says:

"Many interesting ideas and many 'good' experiments have been 'spoiled' by controls. How easy it is to believe that when a result follows a procedure that this result always depends upon that procedure. Propter hoc is very different from post hoc. In asthma, indeed in all the allergic diseases, the danger is greater than usual. This is not only because the nature and cause of the process is still obscure, but particularly because so many different factors can play their parts in it.

"New methods of treatment are particularly open to the risk of a hasty belief in their benefit. We recall our enthusiasm when ephedrine first appeared. Aminophyllin was hailed next. Histamine, given by itself or later in protein combinations, was recommended warmly as a panacea. Now, however, we have learned of its limitations. During this past year or two the antihistamine drugs have been described, extolled, and finally relegated to their proper places. New preparations impress the doctor and they impress the patient. Incidentally, a new doctor means a fresh start and a new hope. Almost every new patient reports his asthma improved during the

first period of treatment, until later he discovers that the new methods are not so fundamental after all.

"New treatments are always welcomed, but none of us can afford to believe at the onset that they are perfect. They deserve to be considered carefully and used with as much intelligence and care as possible. If the controls are good, if other cases treated with placebos do not do just as well, then the truth will appear.

"New theories are essential to our progress. If the theory is good, the evidence in support of it will become readily apparent and available. If, however, the theory is not so good and the evidence behind it is of doubtful value, then the further consideration of it is a waste of time. Ideas are valuable. No advances are made without them, but where the evidence is lacking or where the observations made can be explained quite as easily on some more familiar basis, publication should be withheld. When the evidence can be clarified and displayed in orderly fashion, then progress is made."

Gilman[219] discusses some of the drugs used in allergy, especially the mimetic and so-called lytic drugs. The chemical mediator for the sympathetic nervous system is sympathin which may or may not be chemically identical with epinephrine.

Likewise, the important parasympathomimetic drugs resemble acetylcholine in structure. "Epinephrine is a rather paradoxical drug in that it possesses two types of action, one excitatory, the other inhibitory." The first action causes contraction of smooth muscle, e.g. on musculature of blood vessels to effect arteriolar and capillarly constriction; this constriction of blood vessels of an edematous bronchial mucosa is very desirable as it lessens edema. Unfortunately, this excitatory action on blood vessels is often followed by a prolonged inhibitory action, e.g. after-congestion of mucosa, and in the long run capillary dilatation may occur rather than constriction; this may be the reason for "adrenalin-fastness." The inhibitory action of epinephrine causes relaxation of smooth muscles, both in the alimentary tract and in the bronchial tree, thus increasing the size of the lumina and lessening dyspnea.

Gilman points out that German investigators some six or seven years ago have largely eliminated the excitatory effects of epinephrine and increased the inhibitory action. Isuprel (Aleudrin) is one of these new compounds, made by substitution from the epinephrine structure. It causes a fall in blood pressure rather than a rise; it relaxes bronchi better than does epinephrine, but it does not constrict blood vessels nearly as well as epinephrine. Only prolonged clinical trial will determine the efficiency of Isuprel as compared with epinephrine.

Gilman says the term "antihistamine" drug is a poor one. Epinephrine itself is one of the best of the antihistamine drugs because it is a physiologic antagonist to histamine: histamine dilates peripheral vessels and constricts smooth muscle in the bronchi, epinephrine constricts these vessels and dilates bronchial muscles. The new antihistamine drugs act by blocking; they are not physiologic antagonists of histamine. Their action is similar to that by which atropin can block the effects of acetylcholine or of cholinergic nerve impulses. The term "histaminolytic" would be more appropriate. Gilman also discusses the reasons why antihistamine drugs can prevent histamine shock, but usually fail to prevent antigen anaphylaxis.

Epinephrine is the most important sympathomimetic drug and has stood the test of time since its introduction in 1901. All drugs similar to it must be compared with it both as regards efficacy and drawbacks. Much excellent work, especially as regards treatment of asthma, has appeared.

Lowell and Schiller[317,318,444] have three important papers. They first brought on attacks of asthma in three skin-test negative patients by inhalation with extracts of molds, and birch and ragweed pollens, respectively. Tests with four other potent extracts did not cause symptoms. They used a No. 40 De Vilbiss nebulizer with oxygen flowing through aqueous extracts. In four other patients inhalation of all seven extracts were negative, but inhalation of solutions of histamine or acetylcholine produced sharp pulmonary reactions. They then brought on reductions in vital capacity (0-57 per cent) by inhalation of aerosolized extracts of certain pollens and house dust in ten asthmatic patients. Mild asthma usually resulted, though in some trials a fall in vital capacity occurred without signs or symptoms of asthma. Tests with control solutions and control patients were negative. Lastly, an intravenous injection of 0.48 gm. aminophyllin in three asthmatic patients gave the greatest protection against inhalation asthma; epinephrine 0.3-0.5 c.c. (1:1000) gave definite but incomplete protection; atropine and Pyribenzamine (0.6-1.2 mg., intravenously) were totally ineffective. To restore reduced vital capacity resulting from inhalation of pollen extract, the order of effectiveness was: aminophyllin

intravenously, 5 per cent Isuprel by inhalation, and epinephrine subcutaneously. Atropine and Pyribenzamine were again useless. Atropine, however, decreased the response to Mecholyl, and Pyribenzamine protected against and restored vital capacity due to inhalation of histamine; these results suggest that neither acetylcholine nor histamine are determining factors in production of pollen-induced attacks of asthma.

Excellent papers came from France. Hamburger[237] states that an average normal adult exhales about one liter air per second; asthmatics expire 50 to 80 per cent less, not only in the acute stage, but also when the patient seems symptom-free. He found that aminophyllin was the strongest broncho-dilator, acting directly on bronchial muscles. Epinephrine and isopropylepinephrine (Aleudrin or Isuprel) also prevented broncho-constriction (brought on by histamine or acetylcholine). But, on repetition at short intervals, epinephrine loses about 50 per cent of its effectiveness against acetylcholine, thus duplicating epinephrine-fastness as seen in status asthmaticus. The effect of simultaneous use of two broncho-dilating drugs acting by different mechanisms (epinephrine and aminophyllin) is much greater than the sum of the effects of each drug used alone.

Hamburger, Halpern and DeGeorges[240] elaborate on their method of testing the average expiratory rate. They use a spirometer like that for vital capacity, but the patient is told to blow out the air as quickly and completely as he can, and the expiration time is measured with a chronometer. In asthmatics the rate is markedly lowered, usually about 20 to 40 per cent of the normal rate. It usually remains low between spells even when there is no other clinical evidence of asthma. In emphysema and pneumothorax the expiratory rate is normal, even when vital capacity is much reduced. The test, therefore, is simple and clinically valuable.

In support of his paper,[237] Hamburger, Milliez and Halpern[239] connected the trachea of an animal with an apparatus giving a very accurate continuous recording of the bronchial tonus. A constant dose of acetylcholine is injected every third minute, producing each time a sharp and brief increase of bronchial tonus. The animal is then given epinephrine, ephedrine or Aleudrin either intravenously or by aerosol. At first, the broncho-constricting effect of acetylcholine is completely obviated. Then, as the effect of the sympathomimetic drug wears off, the broncho-constricting effect reappears. Eventually, in 70 per cent of the cases, the constriction caused by acetylcholine becomes greater and may reach a two-fold increase before again decreasing to the same level as before the use of the sympathomimetic drug. This is experimental duplication of epinephrine-fastness observed in status asthmaticus. The authors believe that this phenomenon actually is, in many cases, the direct cause of status asthmaticus. Such a reversed effect is never observed experimentally with aminophyllin and this is in keeping with its excellent clinical results in status asthmaticus. [This work should increase our caution in over-use of epinephrine and similar drugs, especially in status asthmaticus. We, too, have noted much better results in status asthmaticus from aminophyllin than from epinephrine, and have found, as have others, that epinephrine usually regains its value after a few days of avoidance.] In another paper,[238] the same authors give clinical evidence of the effectiveness of aminophyllin and the dangers of increased asthma from an excess of epinephrine, in addition to danger from possible angina, hypertension and possible sudden death. Davy and Thibault[148] studied the action of some new amines which oppose the action of epinephrine on the bronchi.

Castillo and DeBeer[104] sectioned the trachea of guinea pigs into twelve muscular rings of approximately the same widths and tied these rings together to form a chain. The minute changes brought on by bronchoconstrictor and dilator drugs are thereby greatly magnified. The tracheal reactions parallel those of the bronchial muscles in guinea pigs. Epinephrine, aminophyllin and papaverine dilated tracheal muscle, proportional to the dose used. Atropine, Novatropin, Syntropan, Transentin, and Benadryl caused no relaxation and did not relieve spasm induced by barium chloride, but did counteract effects of acetylcholine. In large doses Benadryl contracted tracheal muscle despite the striking antagonism of this drug on histamine-induced contraction.

Isuprel (Aleudrin), now in use for several years, is a better broncho-dilator than epinephrine from which it was manufactured. But it is less efficient in constricting blood vessels and therefore has much less effect against bronchial edema than has epinephrine. Segal and Beakey[452,454] found the drug effective in relieving the dyspnea of bronchial asthma; the lower the vital capacity the greater the degree of relief. Variation in the systolic and diastolic readings in inspiration and expiration were decreased, and undesirable pressor effects and tachycardia were minimal and corresponded to the patient's tolerance to sympathomimetic amines.

The drug should not be given intravenously, nor should more than 0.5 c.c. of the 1:1000 dilution be injected subcutaneously. Sensitive patients should be started on inhalatory doses of 0.5 c.c. of the 1:200 dilution and subcutaneous doses of 0.1 c.c. of the 1:000 dilution, gradually increasing to individual tolerance. Patients in the epinephrine-fast state did well and no fastness to Isuprel was observed. The drug was tried 187 times in eighty-two ambulatory patients by oxygen aerosol and in forty hospitalized patients treated by one or both routes. They also gave tablets of Isuprel to nine patients. It may be good in mild asthma but it is slower in action and, in doses of over 50 mg. causes much nervousness.

Charlier[111] obtained excellent symptomatic relief in 200 patients who had dyspnea from such diseases as bronchial asthma, pulmonary emphysemas of varying degrees, with or without heart failure and cor pulmonale, asthmatic bronchitis and silicosis. A mixture of Aleudrin, Idrianol and novacain was inhaled daily with regular relief of dyspnea. These drugs induce "pneumodilatation," acting synergistically, and in case of circulatory insufficiency they improve cardiac function by increasing oxygenation, cardiac output, and the "analeptic action of Idrianol on the cardiovascular system." Three typical case reports are presented. Such aerosols may also have a prophylactic action, and if used early may prevent the late irreversible effects of silicosis in miners. Charlier,[110] in 197 asthmatic patients, found that if Isuprel is inhaled regularly and in a complete course according to settled rules, excellent results follow in most cases. It is especially good in patients in whom other measures have failed. The article contains an extensive bibliography, diagrams of the apparatus, and tables of results.

Isuprel effectively controls bronchoconstriction and asthma during general anesthesia, say Cohen and Van Bergen.[122] It has little effect on the cardiovascular system, and is non-toxic in therapeutic doses. They recommend 0.5 to 1.0 c.c. of a 1:50,000 solution intravenously during anesthesia, repeated if asthma recurs. They studied seven patients and also noted the bronchodilator and cardiovascular actions of epinephrine, Butanefrin, Benadryl, ephedrine, aminophyllin and Isuprel. Isuprel alone was an effective bronchodilator and yet had little effect on the cardiovascular system. It is particularly indicated in asthmatics who are anesthetized by cyclopropane because this anesthetic may cause some cardiac dysfunction. Siegmund and associates[169] also found Isuprel to be the best bronchodilator in histamine-induced bronchospasm in guinea pigs.

(To be continued in July-August issue, which will include list of references.)

ALLERGENS RESEARCH DIVISION OF THE BUREAU OF AGRICULTURAL AND INDUSTRIAL CHEMISTRY

On May 15, 1949, the Honor Awards Ceremony of the United States Department of Agriculture was held. On this occasion, the Allergens Research Division of the Bureau of Agricultural and Industrial Chemistry received the following citation:

"For outstanding achievement in fundamental chemical and biological research on the allergenic components of agricultural products, which has markedly advanced scientific knowledge of allergens, made possible more accurate methods for the quantitative determination of allergenic activity, and contributed significantly to wider utilization of farm commodities and to the general health and welfare."

Staff members of this unit are: Henry Stevens, Ph.D., Head; Joseph H. Spies, Ph.D., and E. J. Coulson, Ph.D., Biochemists; Dorris C. Chambers, M.S., Chemist; and Harry S. Bernton, M.D., Clinical Specialist in Allergy and Allergist to Providence Hospital, Washington, D. C.

News Items

FIFTH ANNUAL MEETING—ACA

The Fifth Annual Meeting of The American College of Allergists was held at the Palmer House, Chicago, Illinois, April 14-17, 1949. With a registration of over 1,100, this was the largest meeting devoted to allergy that has ever been held.

The success of the meeting is attributed to the untiring efforts of the Program Committee of which Dr. John H. Mitchell was Chairman, and to the Chairman of the Committee on Local Arrangements, Dr. Leon Unger, and his Host Committee who contributed so generously in making the social activities successful. Also, much credit is due Dr. Jonathan Forman who was in charge of all publicity for the meeting.

There were forty Technical Exhibits and fifteen Scientific Exhibits. The Technical Exhibits represented the leading manufacturers of products related to allergy and included the majority of our Sustaining Members. The Scientific Exhibits represented a wide range of graphic demonstrations pertaining to allergy. Undoubtedly, the attendance was greatly augmented by the excellent Technical and Scientific Exhibit.

The program ranged from the fundamental investigations of immunology and allergy to practical clinical investigations, new drugs used in allergy, the psychosomatic factors of allergy, a symposium on cottonseed oil sensitivity and a panel discussion on pediatric allergy.

The Local Committee on Arrangements and the Host Committee composed of members in Illinois and adjacent states, arranged for the luncheon and style show at Marshall Fields, as well as the Breakfast Club Broadcast, for the ladies.

The annual banquet held on Saturday evening, April 16, was well attended. Short talks were presented by the retiring president, George E. Rockwell and the incoming president, Jonathan Forman. The wine for the banquet was generously supplied by Marcelle Cosmetics, Inc., Chicago, Illinois.

Business Meetings

At the business meeting of the Board of Regents, it was decided that the next annual meeting of the College would be held in St. Louis, Missouri. Since then definite arrangements have been made to hold the sixth annual meeting at the Hotel Jefferson, St. Louis, Missouri, January 15-18, 1950. Registration for this meeting will commence at 2 p.m., Sunday, January 15, but there will be no Technical or Scientific Exhibits on Sunday. Monday, Tuesday and Wednesday will be devoted to a Scientific Program, as well as a Technical and Scientific Exhibit.

The Board of Regents voted fourteen members to Active Fellowship at this meeting. During the past year a total of thirty-one members have been voted to Active Fellowship. This list includes: Albert Avedon, M.D., William Harvey Blank, M.D., Sidney H. Carsley, M.D., Pasquale Cioffi, M.D., James F. Clancy, M.D., James E. Culleton, M.D., Ross Dale Dickson, M.D., Erna S. Enderle, M.D., Seymour Fisher, M.D., Arthur A. Goldfarb, M.D., Benjamin F. Gordon, M.D., Dorence O. Hankinson, M.D., Herman A. Heise, M.D., Preston S. Herring, M.D., Harry H. Hershey, M.D., Leo Hochfeld, M.D., Stanislaus H. Jaros, M.D., A. Paul Knott, M.D., Herman M. Lubenstein, M.D., Eugene J. Luippold, M.D., B. Thomas McMahon, M.D., Joseph P. Maher, M.D., Roy R. Matteri, M.D., William L. Mermis, M.D., Ira R. Morrison, M.D., Anthony F. Piraino, M.D., Raymond S. Rosedale, M.D., Alvin Slipyan, M.D., George Knox Spearman, M.D., Gardiner S. Stout, M.D., and Harry R. Weil, M.D.

During the past year the College has been unfortunate in the loss, through death, of the following: George C. Anglin, M.D., Active; Vincent J. Irwin, Jr., M.D., Active; Voyle M. James, M.D., Active; Philip J. Jordan, M.D., Active; William A. Mowry, M.D., Active; Herman Spitz, M.D., Active; and Clarence K. Weil, M.D.,

Active. Obituaries have appeared in the ANNALS OF ALLERGY, and condolences have been sent to the families.

At the general business meeting of the College on Saturday, April 16, the following members were elected to serve the ensuing year:

President-Elect—Dr. John H. Mitchell
First Vice President—Dr. Homer E. Prince
Second Vice President—Dr. John P. Henry
Secretary-Treasurer—Dr. F. W. Wittich
Board of Regents (one-year term)—Dr. Herbert J. Rinkel

A detailed report of the College finances was presented by Dr. Hal M. Davison, Chairman of the Finance Committee. The report was approved as read. The report reads as follows:

Physical Setup of The American College of Allergists, Inc.

We have investigated the space used by The American College of Allergists and our opinion is that as little space as can be used is being used and that this is paid for at the current rate in the city. The space used by The International Association of Allergists is separate from the College. The American College of Allergists does not furnish an office personally for Doctor Wittich or Mrs. Wittich.

The necessary furniture, equipment and supplies used by the College are owned and used by the College.

The salaries of the employes have been broken down and placed in the proper accounts. The one stenographer used by Doctor Wittich personally is paid for by the hour by Doctor Wittich. Any stenographic work for The International Association of Allergists is also paid for by the hour by The International Association of Allergists. Stenographic work for the Quarterly Review of Allergy and Applied Immunology has been computed on an average and is paid for on a monthly basis.

All checks are countersigned by the Assistant Treasurer, Doctor Albert V. Stoesser.

Travel Allowance

The report of the auditor on travel allowance has been broken down with the representative of the auditing company present and it has been analyzed to the last penny. It is agreed by the committee that Doctor Wittich's expenses should be paid to any meeting where he actually represents the College and for the duration of time that he is on College business. These expenses should include car fare, hotel bills, meals and incidental expenses.

Entertainment

It is recognized by the Finance Committee that a certain amount of entertainment of the proper people should be done by The American College of Allergists, but this should be exceedingly limited and should not include officers, the Board of Regents, Fellows, members or employes of the College who may be visiting Minneapolis or present at any of the meetings. We do not feel that set rules may be laid down for this entertainment, but that this must be left to the discretion of the Secretary, himself, when in his opinion it would be for the actual good of the College. It is recommended that the bill for entertainment should not exceed for one year, under any circumstances, $250.00.

It is also recognized by the Finance Committee that Doctor and Mrs. Wittich cannot personally afford to entertain visitors to the home office of The American College of Allergists, nor can the College, and this should neither be expected or accepted, if offered.

Annual Audit

It is requested by the Finance Committee that there be an annual audit of the books and that this include an itemized breakdown of the expenses of the annual meeting, in-

structional courses, travel expenses and entertainment, in addition to those items already broken down.

It is also requested that at this annual audit, the auditor examine the methods of running the office as to its efficiency and that recommendations be made for changes necessary for increased efficiency and economy and that a report of this be included in the audit.

Recommendations

It is recommended to the Board of Regents that:

1. The sale of the 1948 Instructional Courses be put on sale for $5.00 and that the older copies be put on sale for $2.50.
2. A registration fee of $5.00 be made for all non-members at the annual meetings.
3. The printing of instructional courses be discontinued and that, instead, they be mimeographed, with no cuts.

Proposed Budget

The Finance Committee has considered the expense of running the office and recommend the following budget for the ensuing year:

Sinking Fund	$1,706.00
Bruce Publishing Company ($6.00 for each member for ANNALS OF ALLERGY)	5,118.00
Bruce Publishing Company (Progress notes, Bound Volumes)	500.00
Certificate Printing	200.00
Salaries	
1 girl, $2,500 a year	2,500.00
4 girls, $2,400 a year (including Mrs. Wittich)	9,600.00
Dr. F. W. Wittich	1,200.00
Office Supplies and Expense	500.00
Postage	500.00
Rent	1,300.00
Electricity	324.00
Telephone and Telegraph	500.00
Audit and Legal Fees	300.00
Entertainment	250.00
Travel	600.00
Petty Cash (for miscellaneous items too small for checks)	300.00
	$25,398.00

After checking the budget, it is anticipated that further revenues will be made by selling past instructional courses, new members and Fellows, advance of members to Fellowship, more Sustaining Members and the decrease in cost of the instructional courses by mimeographing the outlines instead of printing them.

Our President, Dr. George E. Rockwell, and the Finance Committee as a whole visited Minneapolis for two days and have personally checked the items mentioned above in the presence of a representative of the firm of auditors. The auditor assured the Finance Committee that every check and every voucher for petty cash had been verified and was included in the audit. The expenses of Doctor Rockwell and the Finance Committee for this trip cost the College nothing.

HAL M. DAVISON, M.D., *Chairman*
ALBERT V. STOESSER, M.D., *Assistant Treasurer*
HARRY L. ROGERS, M.D.
BOEN SWINNY, M.D.
F. W. WITTICH, M.D.

A Financial Report of the ANNALS OF ALLERGY was read by the Secretary and accepted.

The following resolutions were adopted by the Board of Directors, the Board of Regents and the College-at-Large:

Resolutions

I. WHEREAS, in many societies there is a tendency over the years to concentrate the administration of the Society in the hands of a few men,
WHEREAS, this practice arises in most instances through the practice of advancing an officer through a succession of positions until finally after seven or eight years he rises more or less automatically to presidency,
WHEREAS, this practice is in the opinion of the Board of Directors a critical mistake in policy in that it only allows about fifty men to serve the Society in fifty years, and thus deprives the Society of the help of many men of ability, and,
WHEREAS, the Board of Directors would regret to see this practice established in our College,
THEREFORE, BE IT RESOLVED that it is the sense of the Board of Directors and it so recommends to the Board of Regents that:

1. No one who has in the past held an elective office in the College should be nominated for another such office, except that all past officers other than past-president, are eligible at any time for consideration in selecting nominations for the presidency—nor does this apply to the office of secretary-treasurer;
2. Physicians recently elevated to or elected to Fellowship in the College should not be considered for an elective office in the College until after a reasonable number of years have elapsed in which such a Fellow may have time to demonstrate his loyalty and ability to the College;
3. A policy be inaugurated, as far as practicable, to spread the offices of the College as widely as possible on a geographical basis;
4. Furthermore, if this program be adopted, it is recommended by the Board of Directors that it be published in the ANNALS OF ALLERGY and that each year the Secretary of the College shall give a copy of these resolutions to each member of the Nominating Committee for his guidance.

II. WHEREAS, from time to time the temptation arises to place past-presidents back on the Board of Regents and thus to limit the number of men who can throughout the years hold office,
THEREFORE, BE IT RESOLVED that it is the sense of the Board of Directors that the By-Laws of the College be changed so that all past-presidents of the College have the right to attend all meetings of the Board of Regents and the privilege of the floor for the purpose of discussion, but no such past-president shall have a vote in the deliberation of the Board of Regents.

Congratulatory cablegrams were read from Dr. Paul Kallós of Sweden and Professor Jimenez Diaz of Madrid, Spain, President of the Spanish Allergy Society. Personal greetings were extended by Doctor Estrada de la Riva, President of the Cuban Allergy Society.

The business meeting adjourned with the introduction of the new president, Dr. Jonathan Forman.

THE INTERNATIONAL ASSOCIATION OF ALLERGISTS

Final arrangements are now being made by Professors A. Grumbach and C. W. Loffler to hold the First International Congress in Allergy of the International Association of Allergists in Zurich in the early fall of 1951. Because of the large number of international congresses which are scheduled for 1949 and 1950, it was decided to postpone the Congress in Allergy until 1951.

The first issue of the *International Archives of Allergy and Applied Immunology*, the official publication of the International Association, is now in press. This is being published by S. Karger, Ltd., Publishers, Basel, Switzerland, and the distributor in this country is Interscience Publishers, Inc., 215 Fourth Avenue, New York 3, New York. The subscription price of $10 per year is included in the annual dues of those members of the IAA who have been able to pay their full dues. All members of the International Association, both Individual Members and Members of any society belonging to the IAA, are invited to submit manuscripts to the Editorial Board for its approval for publication in the new *International Archives*. These may be published in the native language of the various countries. All the allergy societies, which are members of the IAA, have been cordially invited to print their proceedings in the *International Archives*.

NEWS ITEMS

Fourteen of the twenty-three existing allergy societies in the world at the present time are official members of the International Association of Allergists. The British Association of Allergists, of which Dr. Vera B. Walker is President of the Council, has just recently applied to the International Association for affiliation and has been accepted as a society member.

Active Fellows of the American College of Allergists who are interested in joining the IAA as Individual Members should write for information to the Chairman of the Executive Committee, 424 La Salle Medical Building, Minneapolis 2, Minnesota.

1949 FALL GRADUATE INSTRUCTIONAL COURSE IN ALLERGY

The 1949 Fall Graduate Instructional Course in Allergy of The American College of Allergists will be conducted under the auspices of Baylor University School of Medicine, Houston, Texas, October 31 through November 5. This will be a five and one-half day course. Instructors of outstanding ability are already being selected for the faculty. The diagnosis and treatment of allergic diseases, as well as the basic sciences pertaining to allergy, will be presented. Round table discussions will occupy two evenings.

Both members and non-members are cordially invited to attend. The headquarters will be at the beautiful Shamrock Hotel. The price for this course will be $100.00. For reservations write to Mrs. Ellsworth, Shamrock Hotel, Houston, Texas.

CIVILIAN DOCTORS SOUGHT FOR PANAMA CANAL ZONE

Permanent appointments for physicians in the Civil Service now exist in the Panama Canal Medical Service according to an announcement from the Office of The Panama Canal, Washington, D.C.

Starting professional salaries are $5,599 and $6,540 a year, with free transportation to the Canal Zone provided for physicians, their families and household goods. In addition, doctors who receive appointments get two months' paid vacation (including time lost by illness) and reduced fares on Panama Line passenger vessels.

Physicians who are interested in a position as medical officer in the Panama Canal Zone should address their applications to Chief of Office, The Panama Canal, Washington 25, D. C.

DEPARTMENT OF CLINICAL PATHOLOGY AND LABORATORY PROCEDURES

Dr. L. O. Dutton of El Paso, Texas, who has charge of the Department of Clinical Pathology and Laboratory Procedures, in the ANNALS, is very desirous of having members of the College send in material for this department. If you have a new laboratory procedure which applies to allergy or clinical pathology, Doctor Dutton and the members of the Editorial Board will greatly appreciate your submitting the procedure directly to Dr. L. O. Dutton, 616 Mills Building, El Paso, Texas, for editing. In the past, suggestions from this department have been very valuable, and it is hoped that interest will continue.

CALIFORNIA SOCIETY OF ALLERGY

A successful meeting of the Allergy Section of the California Medical Association and the California Society of Allergy was held May 8 and 9 at the Biltmore Hotel, Los Angeles, California. On May 8 there was a joint meeting of Allergy, General Medicine and General Practice Sections. The Allergy Section Meeting of the California Society of Allergy was held on May 9 followed by a dinner meeting that evening.

NEWS ITEMS

CONNECTICUT ALLERGY SOCIETY

The second annual meeting of the Connecticut Allergy Society was held on May 4, 1949, in New Britain, Connecticut, in conjunction with the annual meeting of the Connecticut State Medical Society. Doctor Matthew Walzer of Brooklyn, New York, spoke on "Management of Bronchial Asthma". It was a very stimulating and instructive paper and brought forth considerable discussion. The meeting was extremely well attended by members of the Society and guests.

A business meeting preceded the clinical session at which time the election of officers took place. Sidney W. Jennes, Waterbury, was re-elected President, Barnett Freedman, New Haven, Vice-President, Russell Webber, Waterbury, Secretary-Treasurer, and Arthur Roche and Vincent Cenci, Hartford, members of the Executive Committee.

ISRAEL SOCIETY OF ALLERGY

The Israel Society of Allergy has been founded and is now limited to Jerusalem but later on will be extended to all of Israel. Officers of the Society are: President, Dr. M. J. Gutmann; Prof. B. Zondek; Prof. G. Witenberg, and Doctor Tass.

LOUISIANA ALLERGY SOCIETY

At the recent meeting of the Louisiana Allergy Society the following program was presented: "The Injudicious Use of Intranasal Medication" by Dr. A. J. McComiskey of New Orleans; "Khellin" by Dr. Vincent J. Derbes of New Orleans; "Orthoxine in Bronchial Asthma" by Drs. Henry D. Ogden and Louis Cullick, both of New Orleans; and "Asthma in Childhood" by Dr. J. Dudley Youman, Jr., of Shreveport. Dr. Henry D. Ogden of New Orleans presided over this meeting.

The following officers were elected: President, Dr. J. Dudley Youman, Jr.; Vice President, Dr. H. Whitney Boggs, and Secretary, Dr. Vincent J. Derbes.

MEXICAN SOCIETY OF ALLERGISTS

The Directive Council of the Mexican Society of Allergists was changed January 29, 1949, and the following members have been elected: President, Dr. Carlos Canseco; Vice President, Dr. M. Salazar Mallen; Secretary, Dr. Julio V. Cueva; Treasurer, Dr. Oscar de la Fuente.

THE NEW JERSEY ALLERGY SOCIETY

Dr. Nathan Schaffer, President of the New Jersey Allergy Society, has made the following announcement.

The New Jersey Allergy Society has formed a Committee on Aerobiology to do an air survey of the state of New Jersey for the purpose of finding allergenic factors not presently recognized. The work will be done in the following fields: Pollen surveys, Bacteria surveys, Fungi surveys, Chemical contaminants, and Meteorology.

With funds supplied by Schering Laboratories, six Wells Air Centrifuges will be set up in widely separated sites in the state. Daily air specimens will be studied. The chairmen for the entire project are Nathan Schaffer, M.D., of East Orange, New Jersey, and Edward E. Seidman, M.D., of Plainfield, New Jersey. Sub-Chairmen are as follows: **Pollen**, L. Byck, M.D., Newark; **Bacteria**, E. Seidman, M.D., Plainfield; **Fungi**, N. Schaffer, M.D., East Orange; **Chemical contaminants**, C. Weston, M.D., Glen Ridge; and **Meteorology**, F. Rosen, M.D., Newark.

The sub-committee on Mycology, which consists of Doctors Schaffer, Seidman, Byck, Suesserman, and Feldman, are attending conferences on Mycology four hours a week at Rutgers University in New Brunswick, under the direction of C. M. Haen-

seler, M.D., and B. H. Davis, M.D., of the Department of Plant Pathology, College of Agriculture. These conferences started with the school term in February, and plans are being made for their indefinite continuance. Doctors Haenseler and Davis will work with this committee in attempting to identify any fungi found in quantity. Extracts of these will be made and sent to all members of the Society for clinical testing and evaluation.

Plans are being made to set up similar conferences in Bacteriology and Pollen identification at Rutgers in the near future.

THE NEW YORK ALLERGY SOCIETY

The following have been elected as officers of the New York Allergy Society: President, Max Grolnick, M.D.; President-Elect, James Barnard, M.D.; Vice-President, Matthew Brunner, M.D.; Secretary, Frederick Brown, M.D.; and Treasurer, Paul de Gara, M.D.

Dr. Jack A. Rudolph of Miami Beach, Florida, has retired from private practice and has accepted a position as senior grade physician, consultant in Internal Medicine and Allergy, with the Veterans Administration. His new address is Veteran Administration, 3300 N.E. Second Avenue, Miami, Florida.

Dr. Alfred J. Weil has announced the opening of his office for the practice of clinical allergy at 106 Franklin Avenue, Pearl River, New York.

CHILEAN ALLERGY SOCIETY

The First Congress of the Chilean Allergy Society was held on January 3 to 6, 1949, at Santiago. Dr. Edo. Diaz Carrasco is President of the Society and Dr. Ricardo Guzman is the Secretary. There was a reception for the Honorary Members of the Society at the session on the first day of the Congress, and the following papers were presented: (1) "Allergy in Clinical Practice" by President Edo. Diaz Carrasco and Prof. Hernan Alessandri, and "Antihistaminics" by the Secretary, Dr. Ricardo Guzman; (2) "Our Experience with Ten Cases of Asthma" by Drs. Migual Hermosilla, Zoltan Bernath and Humberto Richetti; and (3) "A Study of Severe Asthma." "Methods of Practical Therapeutics." "The Use of the Bronchoscope." "The Relation of Allergic Flora in Brazil." Presented by Dr. Jorge Anwandter in the absence of the authors, Drs. Paulo Dias da Costa, J. C. Guimeraes and Th. Vian.

On January 4 the following papers were presented: (1) "The Pathology of the Anatomy of Allergy" by Dr. Hector Rodriguez; (2) "Allergenic Flora of Chile" by Dr. Sr. Juan Ibanez and Dr. Zoltan Bernath; and (3) "Allergy from Molds," presented by Dr. Hugo Donoso and Prof. Hernan Alessandri in the absence of Dr. Fred W. Wittich.

On January 5 the following papers were presented: (1) "Dermatologic Allergy" by Dr. Arturo Mardones; (2) "The Allergy Specialist and the Plant Sensitivity of Chile" by Drs. Alejandro Reyes and Humberto Richetti; (3) "Endocrine Factors in Allergy" by Dr. Rafael Tellez; and (4) "Treatment with Tuberculin and Some Affections Considered Allergy" by Dr. Jorge Anwandter.

This First Congress was well attended and its officers and Program Committee are to be congratulated for its success.

SPANISH ALLERGY SOCIETY

The Spanish Allergy Society has just held its First National Congress in Allergy at Madrid, May 26, 27, and 28, 1949. Prof. Jimenez Diaz, President of the Society, held a reception welcoming the guests on the evening of May 25 at the Hotel Ritz.

NEWS ITEMS

On the morning of May 26 Prof. Jimenez Diaz and Drs. C. Lahoz Marques and F. Lahoz presented a paper on the "Concept, Definition, and Classification of Bronchial Asthma in Spain." The remainder of the day was devoted to a symposium on the subject.

On May 27 there was a lecture on "Allergic Dermatologic Diseases" presented by Profs. Gay Prieto, Gomez Orbanejz and Vilanova, followed by a symposium.

On May 28 Drs. Arjona Trigueros and Ales Reinlein presented a paper on "Anaphylaxis and Allergy. Its Mechanism and Significance" which was followed by a discussion. At the afternoon session there were three discussions of the entire program, which were followed by a dinner at the Hotel Ritz closing the meeting of the First National Congress in Allergy.

AIR FORCE MEDICAL RESERVE IS ESTABLISHED

General Hoyt S. Vandenberg, Chief of Staff, U. S. Air Force, announced today that applications are being received for commissions in the newly created Air Force Medical Reserve. Physicians, dentists, nurses, and other medical personnel who served with the Army Air Forces during the war may make application through the Air Adjutant General, U. S. Air Force, in Washington.

THE QUARTERLY REVIEW OF ALLERGY AND APPLIED IMMUNOLOGY

A notice is hereby given to all subscribers to the *Quarterly Review of Allergy and Applied Immunology* that this publication will be under new management beginning with the June issue. Owing to the many details necessary for this transaction, the June issue will probably not appear until the latter part of July. The new *Quarterly* will be published by the Bruce Publishing Company, publishers of the ANNALS OF ALLERGY. A special combination rate will be available to subscribers to ANNALS OF ALLERGY. The *Quarterly* will be greatly enlarged and will include many more reviews than heretofore. The Editorial Staff is being reorganized, and the names of many notable physicians will be added. The style and format of the *Quarterly* is being completely revised. The reviews will be concise, critical accounts of the publications and will embrace the essential literature on allergy and immunology throughout the world.

IN MEMORIAM

HERMAN SPITZ, M.D., F.A.C.A.

We sincerely regret to announce the death of Dr. Herman Spitz of Nashville, Tennessee, on February 4, 1949. His death was due to heart complications.

Doctor Spitz was born June 29, 1885, in Hungary and received his medical education at Vanderbilt University, graduating from that institution in 1912. Postgraduate work was done at Cornell University and Harvard. For a time he taught at Vanderbilt University. He was a member of the hospital staffs of Woman's Hospital, Baptist Hospital, St. Thomas Hospital and General Hospital of Nashville. Doctor Spitz was a member of the American Medical Association, the American Society of Clinical Pathologists and a Fellow of the American College of Allergists.

Doctor Spitz is survived by his wife, Helene, and one daughter, Mrs. Ruth S. Beck. The members of the College extend their sincere sympathy to the family.

THE TREATMENT OF BRONCHIAL ASTHMA WITH ISUPREL

(Continued from Page 389)

relieved the so-called epinephrine-resistant types of dyspnea. Its side reactions were not as severe as the side reactions of epinephrine.

3. Isuprel orally was the least efficient of this group in the treatment of bronchial asthma.

4. Side reactions so common with this group of Isuprels were not comparatively greater than the side reactions occurring after the use of such other drugs as ephedrine, aminophylline, and epinephrine.

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Suite 406-410
Kenosha National Bank Building

BOOK REVIEWS

TECHNIQUES of HISTO- and CYTO-CHEMISTRY. By David Glick. Pages XXIV plus 531. Price $8.00. New York: Interscience Publishers. 1949.

Dr. R. R. Bensley, who has himself done so much to forward our knowledge of the chemistry of the cell, has written an appreciative foreward to this useful compendium. And compendium it is, for Dr. Glick has assembled a veritable storehouse of apparatus and procedures.

Few books, Lee's *Microtomists Vade Medum* excepted, offer so much help to the reader by assembling all the known methods for a preparation and explicitly giving "cook-book" directions for each. The microscopic or on-the-slide methods of chemical analysis are given in the first section. These are followed by a fully detailed section on the fairyland of microchemistry. Grams become micrograms, burettes become capillary tubes controlled by micrometers, and we are introduced to the fantastic accuracy of the Cartesian diver. Lilliput indeed! A one-entry section on microbiological assay follows to be succeeded by twenty-eight pages devoted to the use of various high-speed centrifuge techniques to biological analysis. Throughout the book are neat and instructive diagrams of apparatus. An extensive bibliography and an index complete the volume, to which has been thoughtfully added a list of manufacturers.

The book is a "must" for all chemically minded microscopists and biological chemists. Treating as it does, a labile and progressing field, we may expect that the author—now on a technique collecting expedition to Scandinavia—will revise the work at frequent intervals. To make it subject to as frequent revision as will be necessary and still find adequate sales, the publishers will probably have to consider a less expensive format, for the book seems somewhat over-priced.

BERRY CAMPBELL, Ph.D.
University of Minnesota

EXPERIMENTAL IMMUNOCHEMISTRY. By Elvin A. Kabat, Ph.D., Associate Professor, College of Physicians and Surgeons, Columbia University, New York, and Manfred M. Mayer, Ph.D., Associate Professor, School of Hygiene and Public Health, The Johns Hopkins University, Baltimore. 567 pages, 88 figures. Springfield, Ill.: Ch.C., Thomas, 1948.

The term "immunochemistry" has become established for the application of exact methods of chemistry and physics in immunology. One may perhaps regret the psychological barrier thus created between a "high brow" and a "low brow" type of immunology. But there is no denying that the men who made the word immunochemistry a badge of academic distinction have made an immense contribution to the revival of immunology during the last twenty years. Their beneficial influence upon the thinking and the techniques of those who may be called the craftsmen of immunology—including the physicians practicing allergy—will be further extended by the present volume. It gives a comprehensive picture of the techniques which have proven so fruitful in the investigation of immunological phenomena.

To those conversant with the immunochemical work of recent years, the names of the two authors are familiar as very active participants in the investigational work in Dr. Heidelberger's laboratory and, more recently, for outstanding work in their own establishments. Their extensive experience is mirrored in detailed and critical descriptions of methods and discussions of their aims, achievements and limitations, which will offer to the beginner as good an initiation as the printed word can convey. The experienced will read the book with pleasure and profit for the sake of

critical appraisal and sound practical advice, not to mention the convenience of having a wealth of data at hand instead of having to unbury them from the library shelves. Access to the original descriptions and to more extensive discussions of the subjects is facilitated by a well-selected bibliography.

The scope of the book is best described by a short review of its table of contents: Part I covers general immunological methods like precipitation, complement fixation, and tests for supersensitivity. Part II treats the applications of quantitative methods, as the estimation of antigens and antibodies, criteria of homogeneity, cross reactions. Part III describes in twenty-three chapters chemical and physical methods, including ultracentrifuge, electrophoresis, and diffusion. There follows in Part IV the techniques of preparing typical compounds, as used in the work of Heidelberger and others, such as crystalline proteins, protein derivatives, microbial carbohydrates, and purified antibody solutions. A concluding section contains a miscellany of data, as on the cleaning and calibration of glassware and animal techniques.

It is hoped that this book will not only find its way to the book shelves of laboratories concerned with investigative and experimental allergy, but that it will also be studiously consulted. It will prove to be a reliable and stimulating friend.

A.J.W.

THE 1948 YEAR BOOK OF EYE, EAR, NOSE AND THROAT. By Louis Bothman, M.D., and Samuel J. Crowe, M.D., with the collaboration of Elmer W. Hagens, M.D. 511 pages. 100 figures. Price $4.75. Chicago: The Year Book Publishers, 1948.

Many new diagnostic and therapeutic procedures applicable to the type of cases seen frequently in practice are offered in this latest volume.

As formerly, there are three parts: (1) the eye; (2) the ear; and (3) the nose and throat. The first chapter contains seventeen articles dealing with all diseases involving the eye, and there are ten articles covering diseases of the ear, nose, and throat.

The Year Book Quiz, consisting of twenty questions, is looked forward to each year since it is a test of one's familiarity with the current literature.

Of particular interest to the allergist is the information that large doses of Vitamin A have a specific therapeutic effect in solar retinitis and that eosinophiles do not occur in a normal conjunctiva, whether there is eosinophilia of the blood or not. The diseased conjunctiva presents eosinophilia in a number of conditions, the commonest of which are typical and abortive vernal conjunctivitis and allergic conjunctivitis. The editors, however, point out that it is much easier to find eosinophiles in the nasal secretions of these patients, and they believe that simple allergic conjunctivitis, abortive vernal catarrh and typical vernal conjunctivitis are of the same origin and vary only in intensity and duration. Molds are incriminated as an etiologic agent even in the "cobblestone" type of vernal catarrh. Allergic manifestations were found (Kjaer-Copenhagen) in 25 per cent of cases of Ménière's disease.

The illustrations, print, and paper stock are excellent.
